POEMS Syndrome: A Rare Case of Monoclonal Plasmoproliferative Disorder

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ABSTRACT

POEMS syndrome is defined by the presence of a peripheral neuropathy (P), a monoclonal plasma cell disorder (M), and other paraneoplastic features, the most common of which include organomegaly (O), endocrinopathy (E), skin changes (S). Not all features of the disease are required to make the diagnosis. We report a case of POEMS syndrome in a 50-year-old female who presented with weakness, abdominal swelling and history of red cell transfusions. Because of the hepatosplenomegaly (Schuffner VII) we diagnosed her as chronic myelocytic leukemia (CML) or myelofibrosis. Her peripheral blood smear did not show granulopoiesis maturation from myeloblast nor leukoerythroblastic feature which was characteristic of CML and myelofibrosis. We found also anemia, peripheral motoric neuropathy and hyperpigmentation at her legs. The protein electrophoresis showed monoclonal gammopathy on β2 globulin. Bone marrow examination showed normal plasma cells. There was no lytic or sclerotic lesion on Schedel and tibia x-ray. The echocardiography showed pulmonary hypertension, pulmonary regurgitation, right and left ventricle hypertrophy with normal ejection fraction (50%). She was treated with melphalan 10 mg/m² (day 1-4) and prednisone 60 mg/m² (day 1-4) every 6 weeks with packed red cells transfusion. After 3 cycles the monoclonal protein was reduced from 35.5% to 26.1% (normal 2-5%) without changes in her spleen size. Until then she continued on melphalan and prednisone treatment. Although POEMS syndrome is a rare disease, it should be considered in patient with hepatosplenomegaly, especially if accompanied by peripheral neuropathy.

Key words: POEMS syndrome, plasma cell, peripheral neuropathy.

INTRODUCTION

POEMS syndrome is defined by the presence of a peripheral neuropathy (P), a monoclonal plasma cell disorder (M), and other paraneoplastic features, the most common of which include organomegaly (O), endocrinopathy (E), skin changes (S). Other names of the syndrome include osteosclerotic myeloma, Crow-Fukase syndrome or Takatsuki syndrome. There are associated features not included in the acronym including sclerotic bone lesion, Castleman disease, papilledema, thrombocytosis, peripheral edema, ascites, effusions, polycythemia, fatigue and clubbing. Not all features are required to make the diagnosis.1,2

Associations between plasma cell dyscrasia and peripheral neuropathy were well recognized as early as the 1950s by Crow. While only 1%-8% of patients with classic multiple myeloma have neuropathy, a third to a half of patients with osteosclerotic myeloma have neuropathy. Moreover, it was found that patients with osteosclerotic myeloma were more likely to have other unusual features, which we now associate with the POEMS syndrome. Hence, a syndrome distinct from myeloma-associated neuropathy came to be recognized. In 1980 Bardwick coined the acronym POEMS.1

Monoclonal gammopathy is commonly caused by myeloma multiple. Because of rare case, POEMS syndromes usually not included in differential diagnosis of patient with anemia, organomegaly and monoclonal gammopathy. In this case report, we emphasize that besides myeloma multiple, there is other disease which should be considered as the cause of monoclonal gammopathy. This is the first case of POEMS syndrome diagnosed in our hospital. We consider this case is important to report for learning the diagnostic approach and treatment of this rare case.
CASE ILLUSTRATION

A 50-year-old female presented with weakness and abdominal swelling for 2 months. She had also a history of 5 unit red blood cell transfusions. On physical examination we found anemia, hepatomegaly, splenomegaly (Schuffner VII) and hyperpigmentation on her legs. There was no papiledema on her eyes. The motoric strength of her legs was 4/4 with reduced physiologic reflex. There were no clubbing fingers. Her hemoglobin level was 6 g%, white blood count 16.300/mm³ and platelet 226.000/mm³. Her liver, kidney, electrolyte were within normal limits. Her blood glucose level showed impaired glucose tolerance. Protein electrophoresis showed monoclonal gammopathy on β2 globulin. She had normal blood viscosity: 4.4 (normal 1.5-4.5). There was no lytic or sclerotic lesion on her Schedel and tibia x-ray. Bone marrow examination showed plasma cells less than 10% with normal morphology. Electromyography showed peripheral neuropathy, axonal demyelinopathy and motoric neuropathy. On echocardiography, we found pulmonary hypertension, pulmonary regurgitation, left and right ventricle hypertrophy with normal ejection fraction (50%).

She was treated with melphalan 10 mg/m² (day 1-4) and prednisone 60 mg/m² (day 1-4) every 6 weeks with packed red cells transfusion. After 3 cycles the monoclonal protein was reduced from 35.5% to 26.1% (normal 2-5%) (Figure 1) without changes in her spleen size. Her hematological findings were hemoglobin 7.4g%, white blood cell 7.700/mm³, platelet 138.000/mm³. Until now she continued on melphalan and prednisone treatment.

DISCUSSION

In middle age patients with huge splenomegaly and anemia, usually we diagnose myeloproliferative disease such as chronic myelocytic leukemia (CML) or myelofibrosis. In our case, although the clinical presentation mimics myeloproliferative disease, the peripheral blood smear does not give the characteristic feature of that disease.

In a Mayo Clinic series of 99 patients with POEMS syndrome, the median age was 51 years (range: 30 to 83) and 63 percent were males. In 2003, Disperzieri et al., published diagnostic criteria of POEMS syndrome. The criteria consist of major and minor criteria. Our patient has 2 major criteria: polyneuropathy and monoclonal plasma cell disorders, 2 minor criteria: organomegaly (liver and spleen), hyperpigmentation and 1 possible associations: pulmonary hypertension.

Table 1

<table>
<thead>
<tr>
<th>Fractions %</th>
<th>Ref. %</th>
<th>Conc.</th>
<th>Ref. Conc.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin</td>
<td>36.0</td>
<td>&lt; 60.0 – 71.0</td>
<td>3.28</td>
</tr>
<tr>
<td>Alpha 1</td>
<td>5.1</td>
<td>&gt; 1.4 – 2.7</td>
<td>0.46</td>
</tr>
<tr>
<td>Alpha 2</td>
<td>8.9</td>
<td>7.0 – 11.0</td>
<td>0.81</td>
</tr>
<tr>
<td>Beta 1</td>
<td>5.8</td>
<td>&lt; 6.0 – 9.0</td>
<td>0.53</td>
</tr>
<tr>
<td>Beta 2</td>
<td>35.5</td>
<td>&gt; 2.0 – 5.0</td>
<td>3.23</td>
</tr>
<tr>
<td>Gamma</td>
<td>8.7</td>
<td>8.0 – 16.0</td>
<td>0.79</td>
</tr>
</tbody>
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A/G Ratio: 0.56 T.P.: 9.1 g/dL

Figure 1. Protein electrophoresis: A. Before treatment; B. After 3 cycles of melphalan and prednisone

Fifty percent of patients in the Mayo Clinic series had organomegaly (hepatomegaly, splenomegaly, or lymphadenopathy). Each was present in about one-fourth of the patients. These figures are lower than those seen in two other major series, in which hepatomegaly, splenomegaly, and lymphadenopathy were present in 68 to 78.35 to 52, and 52 to 61 percent, respectively. Eighty-five percent had a monoclonal protein in the serum.
Osteosclerotic lesions appear in conventional radiographs in 97 percent of patients in the Mayo Clinic study.\textsuperscript{1,2} Forty-seven percent had only sclerotic lesions, 51 percent had mixed sclerotic and lytic lesions, while lytic lesions without evidence of sclerosis were seen in only two percent with bone lesions.\textsuperscript{3}

In the Mayo Clinic series of 137 patients with POEMS syndrome, pulmonary manifestations were present in 28 percent, and included pulmonary hypertension, restrictive lung disease, respiratory muscle weakness, and an isolated diminished diffusing capacity. Significant radiographic findings such as pleural effusion, elevated diaphragm, and increased cardiac silhouette were seen in 28 percent of patients. Respiratory muscle weakness and cough were associated with a poor prognosis.\textsuperscript{4}

The bone marrow plasma cell infiltration is modest (median 5%) and the monoclonal protein (predominantly IgA), with virtually always a light chain, is usually small, frequently requiring immunofixation for its detection.\textsuperscript{5}

Our patient has bone marrow plasma cells less than 10% with normal morphology, but the monoclonal protein (β2 globulin) is detected very high (3.23 g/L).

The cause of POEMS syndrome is unknown, although chronic overproduction of pro-inflammatory and other cytokines (e.g. vascular endothelial growth factor) appears to be a major feature of this disorder.\textsuperscript{7} Although still poorly understood, the pathogenesis of the POEMS syndrome may be related to production by the clonal plasma cells (or their environment) of a combination of soluble factors. These factors resulting in increased vascular permeability and neoangiogenesis. Among various cytokines, vascular endothelial growth factor (VEGF), presumably secreted by plasmacytoma cells or platelets may have a pivotal role.\textsuperscript{6,7} The elevated VEGF level to 3684 pg/mL and 2644 pg/mL was reported in 2 POEMS patients as compared with 471 ± 86 pg/mL in 37 healthy blood donors.\textsuperscript{8}

VEGF contributes to POEMS symptoms by increasing microvascular permeability, which leads to edema, increased endoneural pressure, and exposure of myelin to serum cytokines and complements leading to demyelination.\textsuperscript{9}

The mainstays of therapy are: irradiation or resection of the osteosclerotic lesion, if solitary; alkylator-based therapy (high dose melphalan) and corticosteroid, which should be considered a temporary remedy. Peripheral blood stem cell transplantation is emerging as the most effective therapy, resulting in marked and sustained reduction of VEGF coincident with the clinical improvement.\textsuperscript{5,10} Recently thalidomide, lenalidomide and anti-VEGF monoclonal antibodies have also been used.\textsuperscript{7,11,12}

Jaccard et al reported high-dose therapy (HDT) and autologous blood stem cell transplantation in 5 patients POEMS syndrome with complete responds in 4 patients. Patients were treated as follows: (1) Local radiation was considered in the patients who had a prominent focal bone lesion and was actually performed in 3 patients. (2) Autologous peripheral blood stem cell (PBSC) collection was performed after mobilization by chemotherapy (intravenous cyclophosphamide over 2 days, 60 mg/kg/d) plus subcutaneous granulocyte colony-stimulating factor (G-CSF, 5 mg/kg/d). (3) HDT and PBSC transplantation were performed about 1 month after PBSC collection according to the regimen: high-dose melphalan, either 140 mg/m\textsuperscript{2} (HDM 140) or 200 mg/m\textsuperscript{2} (HDM 200) intravenously.\textsuperscript{8}

Bevacizumab therapy was first reported in 1 patient POEMS syndrome by Badros et al. The regimen consist of melphalan 10 mg/m\textsuperscript{2} intravenously every 28 days for 3 months) and dexamethasone (20 mg orally daily for 4 days every 15 days for 2 months, then monthly afterward); bevacizumab (5 mg/kg intravenously over 90 minutes) was given in months 2 and 3. The drug was well tolerated with rapid reduction in VEGF level (from 2396 pg/mL to 33 pg/mL and was associated with dramatic improvement in all features of the disease, most remarkably the painful neuropathy and edema. Targeting of VEGF with bevacizumab should be investigated further in therapy of POEMS syndrome.\textsuperscript{12}
Dispenzieri et al reported that more than 50% of POEMS syndrome patients had a response to radiation, and 22% to 50% had responses to prednisone and a combination of melphalan and prednisone, respectively. The median survival is 165 months.1

Our patient was treated with melphalan 10 mg/m² PO (1-4) and prednisone 60 mg/m² PO (1-4) every 6 weeks. Until now she had 3 cycles and showed decreased in monoclonal protein level.

CONCLUSION

POEMS syndrome is a rare disease with unknown cause. The pathogenesis of the POEMS syndrome may be related to production by the clonal plasma cells (or their environment) of a combination of soluble factors. Our patient present with polyneuropathy, hepatosplenomegaly, monoclonal gammopathy, pulmonary hypertension and hyperpigmentation which fulfill the diagnostic criteria of POEMS syndrome. Treatment with melphalan and prednisone showed decrease in monoclonal protein level.

POEMS syndrome should be considered as differential diagnosis in patient with hepatosplenomegaly, especially accompanied by peripheral neuropathy.

REFERENCES