Failure of Treatment with Anti-VEGF Monoclonal Antibody for Long-standing POEMS Syndrome

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Abstract

We present the case of a 71-year-old woman with polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes (POEMS) syndrome. Overproduction of vascular endothelial growth factor (VEGF), secreted by plasmacytoma, is considered responsible for the characteristic symptoms, and therefore anti-VEGF monoclonal antibody (bevacizumab) could be a therapeutic option. The patient was treated with bevacizumab 7 years after onset. Despite a dramatic decrease in serum VEGF levels, there was no clinical improvement, possibly because aberrant angiogenesis had already developed systemically. We suggest that careful consideration should be taken for indication of bevacizumab therapy, and this agent may be used in selected patients with a short duration POEMS syndrome.

Key words: POEMS syndrome, Crow-Fukase syndrome, vascular endothelial growth factor, bevacizumab, angiogenesis

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Introduction

Polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes (POEMS) syndrome is a rare cause of peripheral neuropathy with multi-organ involvement (1). Overproduction of vascular endothelial growth factor (VEGF), probably secreted by plasmacytoma, is considered responsible for the characteristic symptoms (2, 3). A number of new therapies, such as autologus peripheral blood stem cell transplantation (3), have recently been tried for suppression of plasmacytoma, and thereby VEGF production. Because VEGF could be a therapeutic target in the disorder, bevacizumab, anti-VEGF monoclonal antibody, has been tried and to date, three patients who received this treatment have been reported (4, 5). However, the results were contradictory; two were successfully treated with bevacizumab (1), whereas in the remaining patient, bevacizumab treatment resulted in no improvement despite a dramatic decrease in the serum level of VEGF (5). These cases with different responses to bevacizumab therapy raise the possibility that this agent is effective for a particular subgroup of patients. Here, we describe a patient with long-standing POEMS syndrome who was treated with bevacizumab treatment, but with no improvement.

Case Report

A 71-year-old woman had gradually developed progressive sensory-motor polyneuropathy, pleural effusion, ascites, peripheral edema, and skin pigmentation and angioma for two years. At the time of the first admission at age 66, laboratory examination showed IgG-κ M-proteinemina, and multiple osteoclastic lesions in the skull, vertebra, and pelvis. Nerve conduction studies showed demyelinating-axonal mixed polyneuropathy; motor nerve conduction velocities were moderately decreased in the median and ulnar nerves, whereas compound muscle action potentials were not recordable in tibial and peroneal nerve studies. She was diagnosed as suffering from POEMS syndrome, and received melphalan/prednisolone therapy for 3 years, resulting in partial remission. Two years after the cessation of the chemotherapy, pleural effusion/ascites, and neuropathic symptoms gradually worsened. She complained dyspnea and inability to walk due to polyneuropathy. The patient was admitted to our hospital 7 years after onset.

Treatment with melphalan (0.24 mg/kg/day for four days) and prednisolone (50 mg/day) was resumed, but her symp-
Figure 1. Sequential findings serum VEGF levels and chest CT before (A), 2 weeks (B) and 6 weeks after (C) intravenous bevacizumab administration (5 mg/kg). Note no improvement in pleural and pericardial effusion despite a dramatic decrease in serum VEGF levels.

In the present case, the decrease in serum VEGF levels induced by bevacizumab administration was not associated with any clinical improvement. There are two hypotheses for the failure of bevacizumab therapy. First, high VEGF can promote aberrant angiogenesis systemically (6). Angiogenesis, when not associated with upregulation of other cytokines such as fibroblast growth factor, would result in immature formation of the basement membrane, leading to development of leaky vessels (6). Under such a condition, bevacizumab can no longer affect vascular permeability. Secondly, cytokines other than VEGF might contribute to the symptoms in POEMS syndrome, but such cytokines have not yet been identified. We therefore think that the former is more likely.

Including the present patient, to date four POEMS patients treated with bevacizumab have been reported; of these, two responded well to this treatment, and the remaining two did not (4, 5). These results do not necessarily eliminate the efficacy of bevacizumab. The present patient had suffered from the disorder for 7 years, whereas the disease duration of the two patients with a good response to bevacizumab was shorter (2 years) (4). In the remaining case, the duration of the disorder was not mentioned (5). It is possible that bevacizumab is effective when administered in the early stage of the disorder before structurally abnormal vessels developed systemically. We suggest that careful consideration should be taken for the indication of bevacizumab therapy, and this agent should be used in selected patients with a short duration POEMS syndrome. Histological examination of the microstructure of the basement membrane of the vessel in a biopsy specimen (e.g., skin) may helpful to determine the indication of bevacizumab therapy, and we would like to do so in a future trial.
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References


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