Successful Treatment with Bortezomib and Thalidomide for POEMS Syndrome Associated with Multicentric Mixed-type Castleman’s Disease

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Polyneuropathy, organomegaly, endocrinopathy, M-protein and skin changes syndrome is a rare multi-systematic disorder of uncertain etiology, if associated with multicentric Castleman’s disease, it can lead to a more serious condition. We here presented a case of polyneuropathy, organomegaly, endocrinopathy, M-protein and skin changes syndrome in a 37-year-old male patient who initially presented with progressive lower limb weakness accompanied by pain, low skin temperature, and hyperpigmentation. He was admitted with increasingly serious dyspnea and lower leg edema. Fluid of serous cavities in the patient were also indicated in ultrasonic inspection and X-ray. Furthermore, biopsy of a left axillary lymph node showed mixed hyaline-vascular and plasma cell type of multicentric Castleman’s disease. Administration of bortezomib (Velcade) (1.3 mg/m² on days 1, 4, 8 and 11 of a 21-day cycle) combined with thalidomide (100 mg/day and 21-day cycle) dramatically improved the condition of this disease. Of note, in our study, combination therapy of bortezomib and thalidomide successfully improved the condition of the patient with polyneuropathy, organomegaly, endocrinopathy, M-protein and skin changes syndrome associated with multicentric Castleman’s disease, suggesting that the combination therapy may be an effective therapeutic strategy for the intractable polyneuropathy, organomegaly, endocrinopathy, M-protein and skin changes syndrome associated with multicentric Castleman’s disease.

Key words: POEMS syndrome – Castleman disease – VEGF – treatment

INTRODUCTION

Polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin changes (POEMS) syndrome is a very rare syndrome probably related to plasma cell dyscrasia. The misdiagnosis of the POEMS syndrome is very common due to its rarity and complicated clinical manifestations. Herein, we presented a case of the POEMS syndrome with an unusual mixed hyaline-vascular and plasma cell type of multicentric Castleman’s disease and fluid of serous cavities in the patient. Dramatical improvement in the physical condition by the treatment with bortezomib and thalidomide was also described.

CASE PRESENTATION

HISTORY

A 37-year-old Chinese male patient was admitted to our hospital because of progressive lower limb numbness and weakness that resulted in inability to walk, accompanied with pain, low skin temperature and hyperpigmentation for 1 year...
and aggravation in 3 months prior to admission. He was admitted with increasing dyspnea, lower leg edema and abdominal distension, and excessive weight loss (10 kg within 3 months). His previous medical history was unremarkable, with no history of diabetes, smoking, alcohol or human immunodeficiency virus (HIV).

**Physical Examination**

Positive physical examination revealed a blood pressure of 168/108 mmHg, lip cyanosis, choked disc, multiple small peripheral lymph nodes, hepatomegaly, splenomegaly, moist rales sounds in the bilateral lower lung, hyperpigmentation, paresthesia in four limbs, distal hypoesthesia of the lower extremities and edema of the lower limbs.

**Laboratory Data**

Laboratory tests on admission showed normal blood count and hypoproteinemia. Urine analysis revealed protein traces (normal, no protein trace), but no Bence Jones’ protein was detected. The level of serum vascular endothelial growth factor (VEGF) was 780 ng/l (normal range, <180 ng/l). The serum interleukin-6 (IL-6) level was 46 pg/ml (normal <5 pg/ml). Screening for HIV and human herpes virus-8 (HHV-8) was negative. HHV-6-nested polymerase chain reaction (PCR) was negative in the blood sample. Erythrocyte sedimentation rate was 30 mm at first hour and hepatitis B virus (HBV) was positive. Anti-nuclear antibodies and rheumatoid factor were negative. Monoclonal IgA(lambda) (7.81 g/l, normal range 0.69–3.82 g/l) was detected in the serum by immunofixation electrophoresis. Endocrinologic investigations showed low levels of T3 and FT3 and a high level of TSH. The ascites in this case were demonstrated as transudate (ascites/serum total protein 42.8%, ascites/serum LDH 52.6% and white cells undetected). Pericardial effusion, bilateral pleural effusion and seroperitoneum were present in the ultrasonic inspection and X-ray. Computed tomographic scans of the patient’s chest and abdomen showed widespread but small lymphadenopathy in the thorax and axilla, and para-aortic area and groin with hepatomegaly and splenomegaly. Electromyography showed axonal loss in the lower extremities with a background sensorimotor demyelinating polyneuropathy.

**Histopathology**

Bone marrow biopsy was considered normal except for an increased number of plasma cells (~6%). Biopsy of a left axillary lymph node was suggestive of mixed hyaline-vascular and plasma cell-type Castleman’s disease (Fig. 1). An immunohistochemical study demonstrated that the majority of germinal centers exhibited a tight/concentric pattern of follicular dendritic cell (FDC) network. Cluster of differentiation (CD)20, CD21, CD35 and CD792 were positive in the FDC. CD38, CD138 and Mum1 were negative in the endochylema.

In conclusion, these clinical and histological findings met the criteria for the POEMS syndrome and multicentric Castleman’s disease.

![Figure 1](image-url)
We treated the patient using bortezomib (Velcade) combined with thalidomide. Bortezomib was administered at a dosage of 1.3 mg/m² on days 1, 4, 8 and 11 of a 21-day cycle. Thalidomide was administered on sleep at a dosage of 100 mg/day and 21-day cycle. Administration of bortezomib with thalidomide was completed after eight cycles. After treatment, the serum VEGF level was 324 ng/l. The serum monoclonal IgA(λ) level was 2.02 g/l. Urine analysis revealed protein traces undetected for 7 weeks before the patient was discharged. Bone marrow biopsy revealed that the number of plasma cells was ~4%. His extravascular volume overload dramatically improved and pleural effusion, ascites and polyneuropathy completely disappeared. In addition, lymphadenectomy was unpalpable and the hepatosplemegaly was alleviated. The patient no longer had numbness or weakness and was able to get back to work. Now, 2 years after the treatment, the patient’s condition remained stable.

DISCUSSION

So far, there are no standard treatment strategies for the POEMS syndrome (1). The traditional therapeutic approach for the POEMS syndrome is immunosuppressive agents and corticosteroids, whereas the response to these drugs is variable. The autologous stem cell transplantation was not planned due to poor performance status and progressive pleural effusion and ascites. The patient in our study was initially treated with high dose of methylprednisolone (80 mg/day) and cyclophosphamide (15 mg/kg, once a week), but his conditions deteriorated after 2 weeks of treatment.

The recent advancement in the study of the pathogenesis of POEMS and Castleman’s disease may help offer more treatment options for the diseases. VEGF is believed to play a pathogenic role in POEMS disease (2,3). Koike and Sobue (4) reported that the VEGF is a cytokine probably secreted by plasma cells and can also be implicated, since it leads to a rapid and reversible elevation of the vascular permeability and is also a growth factor for endothelial cells. VEGF is correlated with the degree of disease activity, and enhanced VEGF levels could explain the organomegaly presented in patients with the POEMS syndrome (5). Thus, in this case with the POEMS syndrome, hepatomegaly, splenomegaly and lymphadenopathy were possibly partially induced by effusion plasma cells. Several reports revealed that the increase in VEGF causes increased vasopermeability leading to the formation of fluid of serous cavities in the patient, which usually presented as effusion. Whereas in this case, the ascites analysis demonstrated a transudate which was probably attributed to hypoproteinemia. In addition, IL-6 is a growth factor present in the bone marrow microenvironment that has an important role in the regulation of the immune response, inflammation, and hematopoiesis (6,7). IL-6 may also be implicated in the pathogenesis of some other lymphoid malignancies and its role in the systemic symptoms of Castleman’s disease has been clearly established (8). Fazakas et al. (9) found that the changes of immune functions induced by HHV-6 may induce the proliferation of polyclonal plasma cells and might be potentially responsible for the development of the Castleman’s disease and POEMS syndrome. However, in this case, HHV-6-nested PCR was negative in the blood sample. Therefore, the role of HHV-6 in the pathogenesis of the Castleman’s disease and POEMS syndrome needs further investigation.

Interestingly, Roccaro et al. (10) found bortezomib (Velcade), a selective inhibitor of proteasomes which restrains the secretion of VEGF and abrogated mediating angiogenesis via dose-dependent inhibition of VEGF and IL-6 secretion by endothelial cells. Moreover, bortezomib has been shown to overcome corticosteroids resistance in myeloma cells (11). Therefore, we decided to apply the combination of bortezomib and thalidomide as the therapeutic approach for the POEMS syndrome associated with multicentric Castleman’s disease. After treatment for eight cycles, the serum VEGF level and the monoclonal IgA(λ) level were decreased. Urine analysis revealed that protein traces were undetected. In addition, lymphadenectomy was unpalpable and the hepatosplenomegaly was alleviated. The extravascular volume overload apparently improved, pleural effusion and ascites completely disappeared, and polyneuropathy gradually improved. Now, 2 years after the treatment, the patient’s condition remained stable.

Recently, the application of bortezomib has been reported in the treatment of POEMS syndrome patients (12,13). Sobas et al. (14) reported that bortezomib was effective in the treatment of refractory form of multicentric Castleman’s disease associated with POEMS. Ohguchi et al. (15) reported successful treatment with bortezomib and thalidomide for the POEMS syndrome. Of note, in our study, combination therapy of bortezomib and thalidomide successfully improved the condition of the patient with the POEMS syndrome associated with multicentric Castleman’s disease. 

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Conflict of interest statement
None declared.

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