CASE REPORT

A case of orthostatic hypotension induced by systemic amyloidosis successfully treated with Bortezomib: infiltration of amyloid proteins into various organs and change of targeted organs by therapy

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Abstract

In some multiple myeloma cases, symptoms of amyloidosis are exhibited more prominently than symptoms of multiple myeloma. These cases are believed to have poorer prognosis compared to those in whom the major symptom is not amyloidosis. On the other hand, the prognosis of patients in whom amyloidosis is associated with peripheral neuropathy is poor, and suitable therapeutics has not been established. In this paper, we report a case of severe orthostatic hypotension as the major symptom associated with systemic amyloidosis. The patient was treated with bortezomib followed by autologous peripheral blood stem cell transplantation. This case was rare in that after relapse; amyloid protein was deposited in different organs, resulting in treatment resistance.

Key words

Amyloidosis, Hypotension, Bortezomib

1 Introduction

In some multiple myeloma cases, symptoms of amyloidosis are displayed more prominently than symptoms of multiple myeloma, and these cases are believed to have poor prognosis [1]. Deposition of amyloid protein is additionally seen in cases of amyloidosis associated with peripheral neuropathy, and is also associated with poor prognosis [2]. In this report, we describe a case of multiple myeloma in which various symptoms of systemic amyloidosis, such as peripheral neuropathy and gastrointestinal dysfunction, had worsened PS (PS4), rendering the patient unable even to sit up. After bortezomib administration, PS improved to PS1, although oral vasopressor administration was also necessary. The patient was then treated with autologous transplantation and entered complete remission after one year and nine months. After this time, amyloid protein was seen to be deposited in organs in addition to those initially containing deposits, and the patient became treatment-resistant. Amyloidosis associated with peripheral neuropathy is associated with a poor prognosis, and

peripheral neuropathy cannot sufficiently be improved with existing chemotherapy methods. Dramatic improvement, however, was observed following bortezomib administration. Moreover, tissue distribution of amyloid protein was altered (by a change in the nature of the amyloid protein), resulting in treatment resistance. This may indicate that a change in distribution of amyloid protein causes treatment resistance, or that bortezomib is effective in systemic amyloidosis associated with peripheral neuropathy.

2 Case report

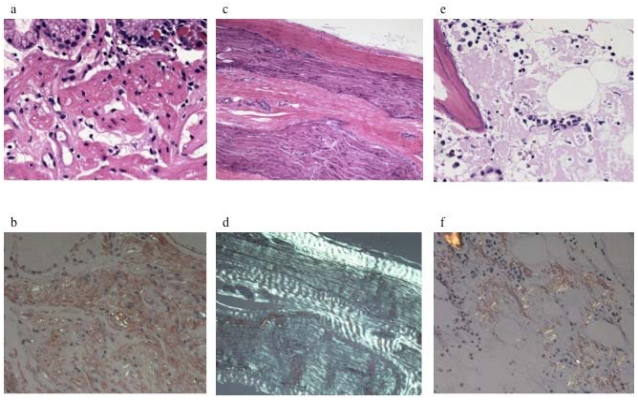

Figure 1. Pathological specimen of initial therapy: a & b) Gastric pathological findings. Polarizing microscopy revealed an abundance of amyloid protein deposition. HE staining; ×400, DFS staining; ×400. c & d) Pathological findings of the gastrocnemius muscle nerve. Polarizing microscopy revealed diffuse deposition of amyloid protein. HE staining; ×200, DFS staining; ×200. e & f) Pathological findings of bone marrow. Polarizing microscopy revealed diffuse deposition of amyloid protein. HE staining; ×400, DFS staining; ×400.

The patient was a 57-year old male who lost consciousness at a systolic pressure of 30mmHg and was taken to the hospital by ambulance on April 25, 2007. The patient was unable to sit up due to orthostatic hypotension, and performance status (PS) was graded at 4. Although IgA was detected in cerebral fluid (9.8 mg/dL: normally 0.4-0.6 mg/dL), plasma cells were not detected, and the patient was diagnosed with orthostatic hypotension due to dysautonomia. IgA-λ protein was detected by serum electrophoresis, and multiple myeloma was suspected. In the Department of Neurology, steroid pulse therapy (methylprednisolone 1g for 3 days) was used for the purpose of improving orthostatic hypotension. On June 4, 2007, bone marrow puncture and biopsy detected an increase in plasma cells in bone marrow (33.6%), and the patient was diagnosed with multiple myeloma. However, deposition of amyloid protein was not detected by this bone marrow biopsy (data not shown). Steroid pulse therapy was not sufficient to improve orthstatic hypotension, and the patient was still unable to sit up. Thereafter, MP therapy consisting of 8 mg/m^2 of melphalan and 40 mg/m^2 of prednisolone was performed, and IgA and β2 micro globulin (β2MG) decreased, however, blood pressure did not improve. An increase in protein was also detected in cerebral fluid, and it was considered that the efficiency of this therapy in the nervous system is low. In consideration of the efficiency of transfer to cerebral fluid, ranimustine (MCNU), which has high penetration into cerebral fluid, was added, and MCNU-VMP therapy consisting of 50 mg/m^2 of MCNU, 6 mg/m^2 of melphalan, 3 mg of vindesine and 60 mg/m^2 of prednisolone was performed. Myeloma cells decreased from 33.6% on to 1.6% on September 19, 2007, with accompanying decreases in IgA and beta2MG, however, orthstatic hypotension did not improve. Attempts were made to raise blood pressure using docarpamine, hydrocortisone, and ameziniumu metilsulfate, but there was no effect. Dysautonomia was suspected due to systemic amyloidosis, and biopsies of the gastrocnemius muscle nerve, bone marrow, and small intestine were performed. Deposition of amyloid protein was detected by Congo red staining (Figure 1. a-f). These amyloid proteins were negative for amyloid A component and positive for P component and were considered to be due to light chain amyloidosis (AL amyloidosis), while bone marrow biopsy showed that the amyloid proteins were positive for the anti-λ antibody and were considered to be AL amyloid proteins. Vascular endothelial growth factor (VEGF) was not detected, and the patient was diagnosed with systemic amyloidosis due to IgA λ type multiple myeloma. Deposition of amyloid protein in the gastrointestinal tract also caused repeated bleeding and gastrointestinal tract dysfunction. Therefore, with an expected effect of bortezomib on the peripheral nerve, 1.3 mg/m^2 of bortezomib [1, 4, 8, 11] and 20 mg/day of dexamethasone (Day 1-4, 8-11) were employed. From the end of bortezomib administration, blood pressure improved from 80s to 110s, and although vasopressor administration was necessary, PS improved to 1.

Because we thought that autologous peripheral blood stem cell transplantation (auto-PBSCT) would be possible together with the improvement of PS, 250 mg/m^2 of etoposide was used to collect autologous peripheral blood stem cells on November 5 of the same year. Blood pressure was maintained over three months, and 140 mg/m^2 of melphalan was then used to conduct auto-PBSCT (iv injection of 2.3 × 10^6/kg CD34+ cells) on February 4, 2008. The cells successfully attached and the patient was discharged on February 18, 2008. In July 2009, blood pressure was around 130mmHg and PS was 0, and vasopressor therapy was terminated. A bone marrow biopsy showed significant deposition of amyloid protein prior to bortezomib treatment. Bortezomib treatment reduced the amyloid deposition, and auto-PBSCT completely diminished it. While the light chain could not be detected, immunoelectrophoretic analysis showed negative expression of IgA λ protein.

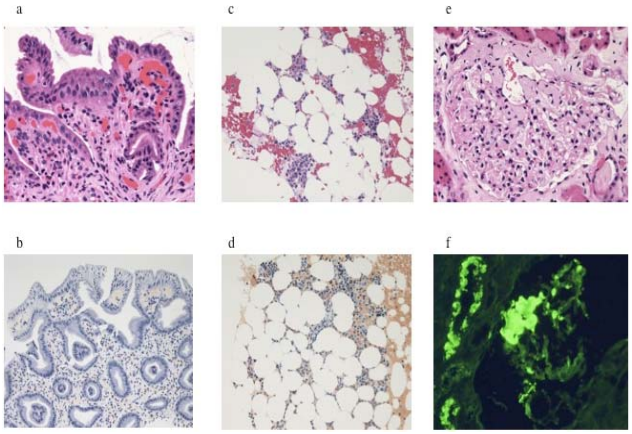

Figure 2. Pathological specimen after symptom relapse: a & b) Gastric pathological findings. Polarizing microscopy failed to detect any amyloid protein deposition. HE staining; ×400, DFS staining; ×400. c & d) Pathological findings of bone marrow. Polarizing microscopy failed to find any deposition of amyloid protein. HE staining; ×400, DFS staining; ×400. e & f) Pathological findings of the kidney. Immunostaining with anti-λ-chain antibody revealed that amyloid protein was deposited in the perivascular region. Electron microscopy confirmed that the deposition was amyloid protein. HE staining; ×400, DFS staining; ×400.

Although the patient did not show any significant symptoms during the duration of the follow-up, immunoelectrophoretic analysis on November 2, 2009 detected expression of IgA λ protein once again. A bone marrow biopsy on January 25, 2010 showed an increase in myeloma cells to 7%, and it was determined that the case had relapsed. Administration of zoledronate was initiated in February 2010, and bortezomib (1.3 mg/m^2, once per week) in April 2010, however, IgA gradually increased. Judging this as a worsening of the condition, 1.3 mg/m^2 of bortezomib [1, 4, 8, 11] was initiated on May 11, 2010. IgA was found to be 574 mg/dL on April 22, 2010, and improved to 160 mg/dL by May 27, 2010. Orthostatic hypotension relapsed during bortezomib therapy, however, and the condition worsened to performance status 4 (PS4). Assuming the existence of amyloidosis, a bone marrow biopsy was performed, however, there was no indication of the deposition of amyloid protein (June 8, 2010), which had been detected prior to the initial treatment (Figure 2 a-d). Because nephrosis was seen, a kidney biopsy was performed and complications from kidney amyloidosis were confirmed. Although a biopsy of the gastrocnemius muscle was performed, the sample did not contain nerve tissue, and nerve deposition of amyloid protein could not be clearly established (Figure 2. e, f). Echocardiography performed on July 8, 2010 showed that thickening of the myocardial wall was mild, and there was no observation implying cardiac amyloidosis. Myeloma cells comprised 0.8% on June 8, 2010, and never exceeded 1% in bone marrow. Based on these observations, it was determined that although deposition of amyloid protein was the major symptom, the condition of amyloidosis was worsening. We therefore planned autologous transplantation, and 50 mg/2days of cyclophosphamide was orally administered until commencement of the transplantation. An echocardiography performed on August 4 prior to autologous transplantation showed that the thickening of the myocardial wall had worsened along with a decrease in diastolic capacity of the cardiac muscle, and cardiac amyloidosis was suspected. Pretreatment with 100 mg/m^2 of melphalan for 2 days was performed from August 30, 2010, and autologous transplantation was performed on September 2. After autologous transplantation, the cells had attached by September 12, however, following this, orthostatic hypotension, nephrosis (due to amyloidosis), and thickening of the myocardial wall never improved. Therefore, administration of 100 mg/day thalidomide was initiated on October 2, which resulted in stoppage in the thickening of the myocardial wall. Orthostatic

hypotension never improved, however, and blood pressure was unable to be maintained, causing the patient to pass away from cardiopulmonary arrest on November 3, 2010.

3 Discussion

Many cases of peripheral neuropathy induced by multiple myeloma are often characterized by pain and neuropathy by pressure to the spinal cord induced by bone lesion crush, and deposition of light chain is observed in both IgM or IgG-k types [1]. Overall, deposition-induced neuropathy is believed to be mild. Peripheral neuropathy induced by deposition of amyloid protein after the onset of multiple myeloma has also been reported. Deposition of amyloid protein in peripheral nerve in multiple myeloma is rare, and it has been suggested that such cases are treatment resistant [2, 3]. In the case reported here, significant deposition of amyloid protein was observed, and blood pressure could not be maintained. In addition, IgA was detected in cerebral fluid, and there was an observation suggesting the influence of amyloid protein on the central nervous system. In cases such as this, PS cannot be maintained and patients have difficulty in urinating and having bowel movements without aid, and it is thought that the prognosis is poor because of difficulty in infection prevention by self-care [4]. Therefore, in this case, with the aim of improvement of PS to less than 1, existing chemotherapy with melphalan and predonine was initially performed. As a result, M protein decreased and beta2MG improved, however, blood pressure in the sitting position could not be maintained at 70 mmHg even though vasopressor was administered. Myeloma cells also decreased after MP and MCNU-VMP therapies, and amyloid proteins decreased, indicating that there were some therapeutic effects; orthostatic hypotension, however, did not improve. Since free light chains (FLC) were not measured in this case, it is not clear whether fluctuations in FLC had any effect, although it cannot be ruled out. In fact, there are cases when FLC fluctuates in the myeloma after therapy and the symptoms do not improve, but after bortezomib administration, however, FLC values quickly improve, resulting in relief of symptoms [5]. It was observed in this case also that immediately after treatment, blood pressure in the sitting position became stable at around 90 mmHg, and the self-management of bowel movements and urination also became possible. Thus, it is possible that bortezomib quickly lowered the unstable FLC levels, resulting in the relief of symptoms. In this case, the occurrence of amyloid protein in the central nervous system, particularly in cerebral fluid, was suggested, which disappeared after treatment with bortezomib. Penetration of bortezomib to cerebral fluid is not high [6, 7], therefore it is likely that production of M protein was suppressed by the systemic effect of bortezomib on myeloma, resulting in disappearance of abnormal protein in cerebral fluid.

In 23% of AL amyloidosis preceded by multiple myeloma, amyloid protein is deposited in multiple tissues. The five-year survival rate is only 20%, and most patients die within 1 year [2]. The median survival period of systemic amyloidosis associated with peripheral neuropathy is 29 months, which is clearly shorter than the median survival period of 60 months for other types of systemic amyloidosis, indicating poorer prognosis [3]; a likely occurrence in this case as well. It is likely that a decrease in peripheral neuropathy caused by bortezomib enabled autologous transplantation, which contributed to life extension.

In this case, however, although multiple myeloma relapsed, the main symptom of the relapse consisted of a worsening of AL amylodosis. Peripheral neuropathy represented by orthostatic hypotension again had occurred. However, deposition of amyloid protein was not detected in the gastrointestinal tract or bone marrow where amyloid protein was initially deposited. Instead, new deposition of amyloid protein was observed in kidney and heart. On the other hand, since kidney biopsy was not performed during the first check-up, it is possible that there were amyloid protein deposits in the kidney from the beginning. Amyloid deposits in the marrow and particularly in the gastrointestinal tract were not detected after the first autologous peripheral blood stem cell transplantation and even after the relapse. Also, there were no changes in the myocardial wall that were detected by ECG since the first check-up, after the autologous transplantation, and until the relapse. Immunoelectrophoresis also showed that the serum and urine were negative for light chains. And hypertrophy of the myocardial wall progressed relatively quickly after relapse. All these observations suggest that the amyloid proteins during the first check-up could be similar to those detected during relapse after the first autologous transplantation and

were falsely detected. The reason for the change in distribution of amyloid protein is not clear, however, we speculate that changes in the nature of amyloid protein might have disrupted bortezomib and autologous transplantation, which resulted in reduced peripheral neuropathy initially. It is possible that the clone producing the abnormal proteins may have been altered. Recently, several lines of evidence suggest diversity in the structure of amyloid protein [8-10]. Moreover, the possibility that the difference in structure of amyloid protein may cause organ affinity has been indicated [10]. In this case, deposition of amyloid protein was observed in heart, nerve, and kidney. In the report by Enqvist et al., such deposition of amyloid protein was not observed, suggesting that a different kind of amyloid protein was involved in this case. Unfortunately, we were unable to analyze structural changes in amyloid protein to verify this. Taken together, it is likely that in this case the structure of amyloid protein was altered either by bortezomib, chemotherapy, autologous transplantation, or by the change in nature of the myeloma itself, resulting in alteration of organ affinity for amyloid protein.

It is thought that the effect of bortezomib on deposition of amyloid protein is approximately 50-80%, including 15-20% of cases involving complete remission [11-14]. Median time to first response was 1.2 month, and median time to complete response (CR) was 2.3 month in bortezomib therapy [14]. In this case, effect of bortezomib also appeared rapidly at the end of the administration of bortezomib. These rapid positive effect is expected improved the prognosis of AL amyloidosis. Recently bortezomib, dexamethasone with cyclophosphamide therapy (CVD) was reported. In this report showed promising result of the response rate was 81.4% that include CR in 41.9%. On these patients, 74% had cardiac involvement [15]. Additionally, Tamaki et al. reported improved heart function following bortezomib administration in a case with deposition of amyloid protein in heart muscle [11], suggesting that bortezomib could be effective for cases of multiple myeloma associated with amyloidosis. On the other hand, bortezomib shows Grade III cardiac toxicity in cases associated with amyloidosis in heart, indicating a side effect concern. In this case, orthostatic hypotension induced by peripheral neuropathy was improved by bortezomib treatment, which allowed autologous transplantation. No obvious peripheral neuropathy induced by bortezomib was observed, however, the possibility that peripheral neuropathy could be displayed intensely in cases with deposition of amyloid protein in peripheral nerve remains to be addressed. In addition, bortezomib or autologous transplantation was not effective after relapse, possibly due to a change in the structure of amyloid protein. Taken together with the fact that multiple myeloma associated with amyloidosis is associated with a poor prognosis, maintenance treatment with thalidomide or consolidation therapy after transplantation may be effective. This possibility remains to be addressed.

4 Conclusion

Multiple myeloma associated with systemic amyloidosis is associated with poor prognosis. However, prognosis could be improved by a combination of Bortezomib, autologous transplantation, and maintenance therapy. Bortezomib could be effective for peripheral neuropathy induced by deposition of amyloid protein. Additionally, a change in amyloid protein structure may cause deposition in different organs, which could be an index of treatment resistance; therefore active attempts to detect amyloid protein are desirable.

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