

[ CASE REPORT ]

# Successful Autologous Hematopoietic Stem Cell Transplantation Followed by Bortezomib Maintenance in a Patient with Relapsed CD138-low Multiple Solitary Plasmacytomas Harboring a 17p Deletion

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## Abstract:

Solitary bone plasmacytoma (SBP) tends to progress to multiple myeloma (MM); however, progression to multiple solitary plasmacytomas (MSP) is rare. We report a case of CD138-low MSP with 17p deletion in a patient with relapsed SBP. 17p deletion is associated with a poor outcome in patients with MM, and the low expression of CD138 in myeloma cells is associated with drug resistance and a poor prognosis. The patient was successfully treated with bortezomib plus dexamethasone induction therapy and autologous hematopoietic stem cell transplantation followed by bortezomib maintenance therapy. Consequently, bortezomib treatment was stopped and a stringent complete response has been maintained.

**Key words:** multiple myeloma, plasmacytoma, CD138, proteasome inhibitor, p53, autologous hematopoietic stem cell transplantation

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## Introduction

Solitary plasmacytoma accounts for 5-10% of all plasma cell neoplasms and occurs more commonly in men than in women (2:1) (1). The International Myeloma Working Group classifies plasmacytomas into solitary bone plasmacytoma (SBP), extramedullary plasmacytoma, and multiple solitary plasmacytomas (MSP) (2). MSP occurs in up to 5% of patients with SBP (2). Radical radiotherapy with or without surgery is recommended for the treatment of SBP; however, an effective treatment strategy has not been established for patients with MSP (2, 3). Autologous hematopoietic stem cell transplantation (auto-HSCT) was previously shown to be effective for improving overall survival in patients with high-risk plasmacytoma (4). Patients who were considered to be at high risk of evolution to multiple myeloma

(MM) were included in the study; however, a risk classification based on a cytogenetic analysis was not used (4). Radiotherapy plus adjuvant chemotherapy and the use of novel-agents have not improved survival in patients with solitary plasmacytoma (5).

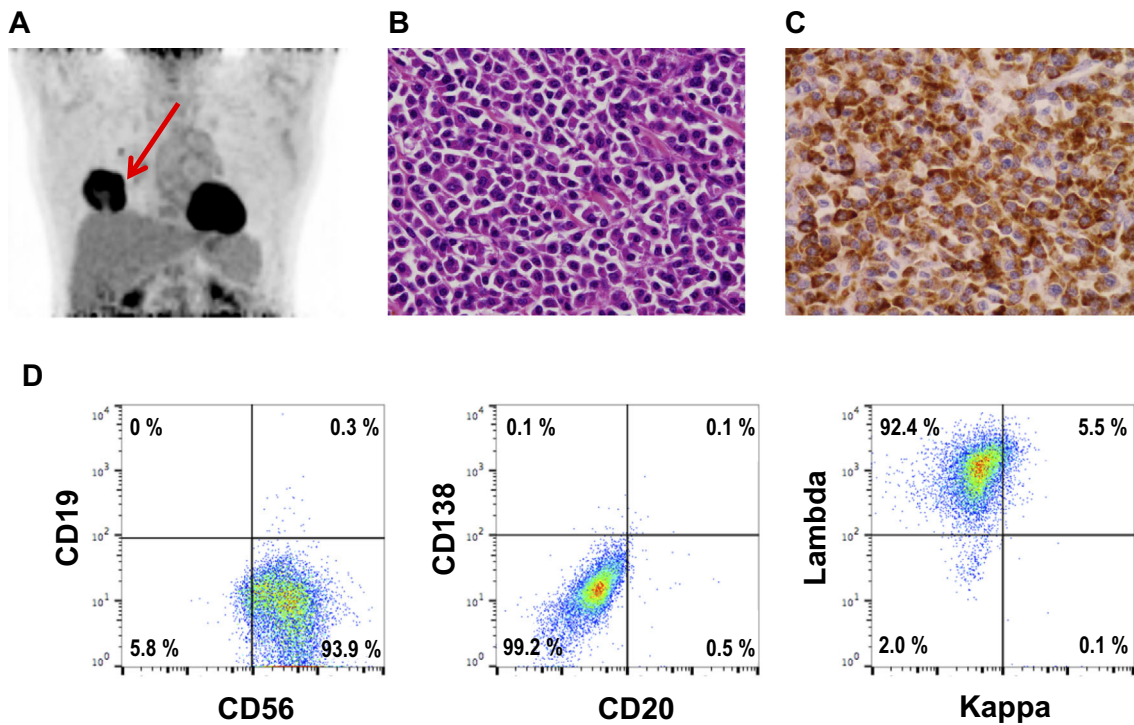
17p deletion is a predictor of short survival in patients with MM (6). Recent studies suggest that the low expression of CD138 in myeloma cells is associated with an immature phenotype, drug resistance, and a poor prognosis (7, 8). However, due to the rarity of plasmacytoma, no definitive prognostic factors with genetic abnormalities resembling MM have been identified to date and no novel agent-based maintenance therapies after auto-HSCT have shown efficacy in the treatment of plasmacytoma.

We herein report a case of relapsed CD138-low MSP with 17p deletion. The patient received bortezomib plus dexamethasone induction therapy and auto-HSCT followed by

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**Figure 1.** The findings of solitary plasmacytoma at the first relapse. **A:** PET-CT showed the increased accumulation of  $^{18}\text{F}$ -FDG in the mass in the right chest (arrow). **B:** Hematoxylin and Eosin staining of the mass (magnification 400 $\times$ ). **C:** Immunohistochemical staining with anti-CD38 antibody (magnification 400 $\times$ ). **D:** The characterization of the cells by flow cytometry. The CD38 $^{+}$  gated cells were subjected to two-color flow cytometry using antibodies specific for CD19 and CD56 (left plot), CD138 and CD20 (middle plot), or intracytoplasmic lambda and kappa (right plot). The CD38 $^{+}$  gated cells were CD19 $^{-}$ CD20 $^{-}$ CD138 $^{\text{low}}$  CD56 $^{+}$ .

bortezomib maintenance therapy, and a stringent complete response (sCR) was achieved.

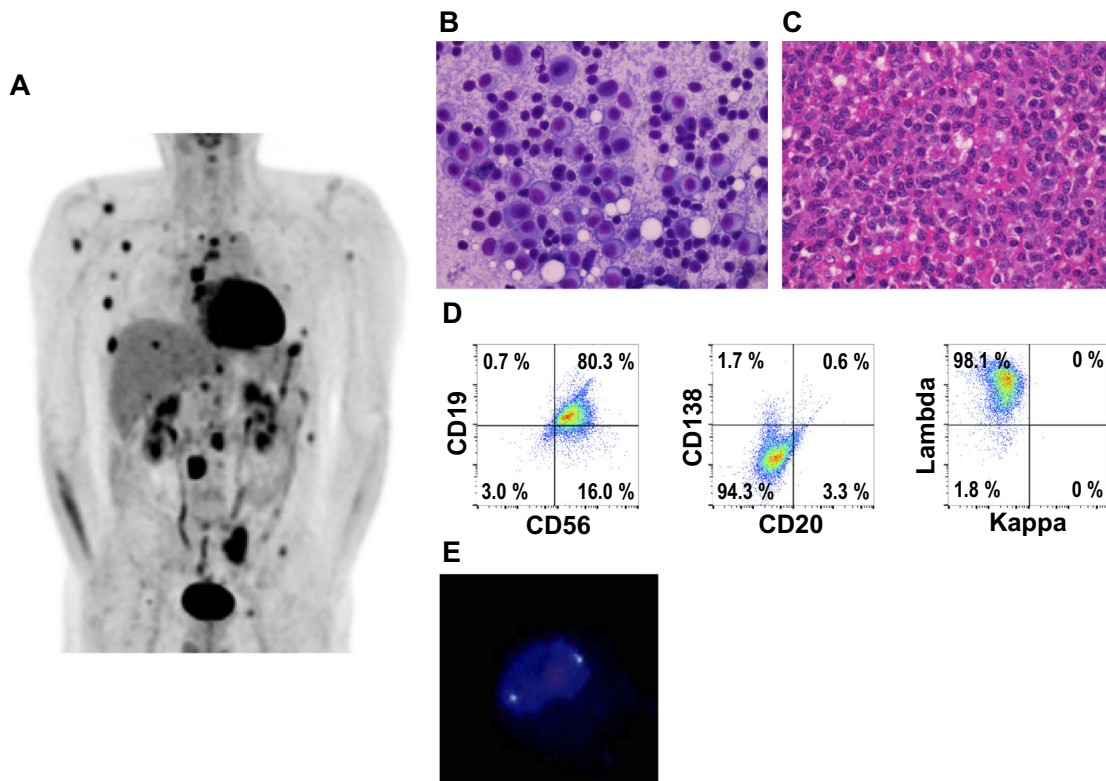
### Case Report

A 55-year-old man presented to our hospital with a mass in the right anterior chest. He was diagnosed with IgG- $\lambda$  type solitary plasmacytoma of the right third rib at 44 years of age and received radiotherapy. At presentation, his IgG level was slightly elevated (2,091 mg/dL, normal range: 861-1,747 mg/dL), and IgG- $\lambda$  type M protein was detected by immunoelectrophoresis.  $^{18}\text{F}$ -fluorodeoxyglucose ( $^{18}\text{F}$ -FDG)-positron emission tomography/computed tomography (PET/CT) showed the increased accumulation of  $^{18}\text{F}$ -FDG in the mass on the right fifth rib (SUV max: 10.36, Fig. 1A). The mass was completely resected and the patient was diagnosed with a relapse of IgG- $\lambda$  type plasmacytoma (Fig. 1B and C). Flow cytometry showed that CD38-gated cells were positive for CD56 and lambda, but negative for CD19, CD20, CD138, and kappa (Fig. 1D). A chromosomal analysis was difficult to perform because of the low proliferative rate of cells. We did not perform a fluorescence *in situ* hybridization (FISH) analysis to detect t(4;14), t(14;16) and 17p deletion. Bone marrow aspiration and biopsy revealed no evidence of clonal myeloma cells.

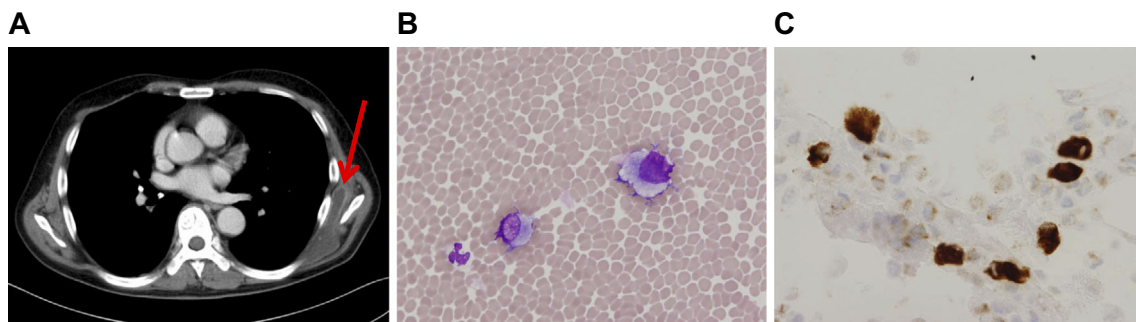
At 2 years after resection, the patient presented with pain

in the bilateral lower ribs of the rib, and blood tests showed an elevated level of IgG (4,235 mg/dL). PET/CT showed the increased accumulation of  $^{18}\text{F}$ -FDG in multiple lymph nodes (Fig. 2A). A right axillary lymph node biopsy was performed and CD138-low IgG- $\lambda$  type plasmacytoma was histopathologically diagnosed (Fig. 2B-D). Flow cytometry showed the increased expression of CD19. A FISH analysis revealed 17p deletion (Fig. 2E); fusion signals of t(4;14) and t(14;16) were not detected. Bone marrow aspiration and biopsy revealed no evidence of clonal myeloma cells. Based on these findings, a clinical diagnosis of relapsed CD138-low MSP with the deletion of 17p was made.

The patient was treated with bortezomib plus dexamethasone induction therapy [BD: bortezomib (1.3 mg/m $^2$  on days 1, 4, 8, and 11, by intravenous infusion) and dexamethasone (20 mg/day, orally on days 1, 2, 4, 5, 8, 9, 11, and 12 for cycles 1-2; and days 1, 2, 4, and 5 for cycles 3-8 in a 3 week cycle)] (9, 10) and a partial response (PR) was achieved after four cycles. Thereafter, progenitor cell mobilization with granulocyte colony-stimulating factor alone and progenitor cell apheresis were successfully performed. However, at 1 month after apheresis, he noticed a soft mass of 10 cm in the left lateral scapula. Contrast CT showed a flat cyst with peripheral enhancement in the left lower scapula, which was suspected to be an exacerbation presenting as a bursitis-like lesion (Fig. 3A). A small amount of bloody



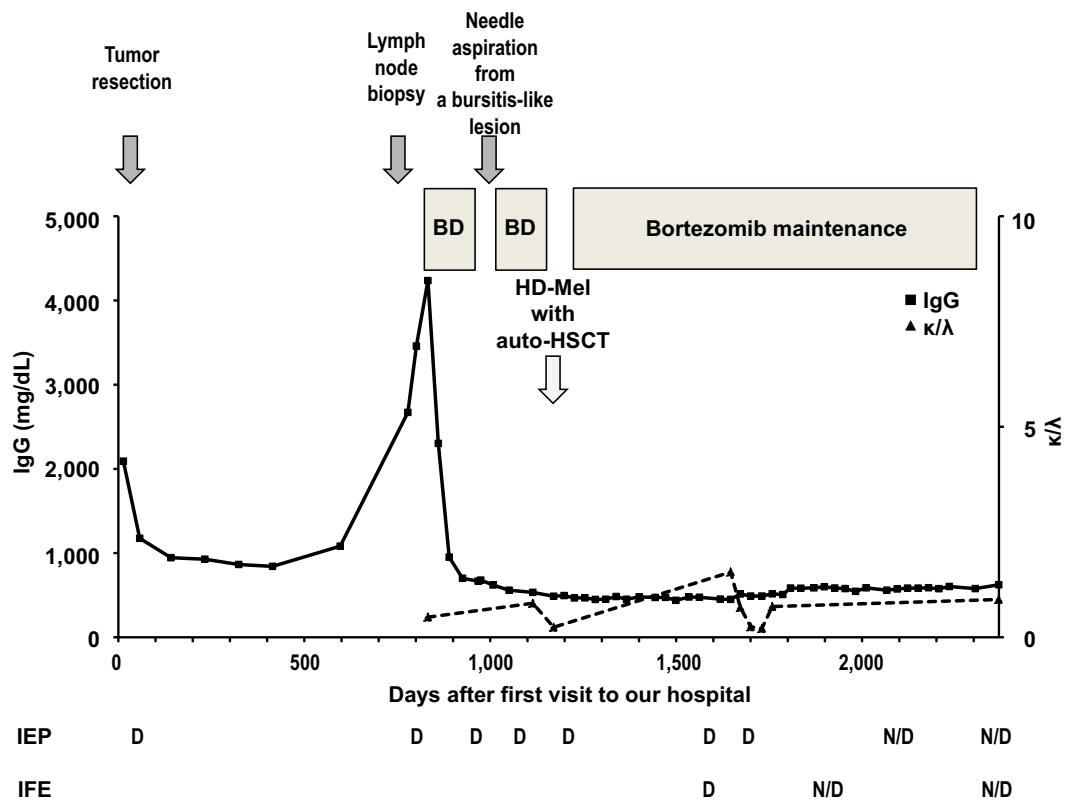
**Figure 2.** The findings of relapsed plasmacytoma at the second relapse. A: The accumulation of <sup>18</sup>F-FDG in multiple lymph nodes. B: May-Giemsa staining of a stamped specimen of the lymph node (magnification 400×). C: Hematoxylin and Eosin staining of the lymph node (magnification 400×). D: Characterization of the cells by flow cytometry. The CD38<sup>+</sup> gated cells were subjected to two-color flow cytometry using antibodies specific for CD19 and CD56 (left plot), CD138 and CD20 (middle plot), or intracytoplasmic lambda and kappa (right plot). The CD38<sup>+</sup> gated cells were CD19<sup>+</sup>CD20<sup>-</sup>CD138<sup>low</sup>CD56<sup>+</sup>. E: 17p deletion was identified by interphase FISH. FISH with a p53 probe on the interphase nuclei. No p53 signal (red) was detected.



**Figure 3.** A bursitis-like lesion emerged after four courses of BD therapy. A: Contrast-enhanced CT showed a flat cyst with peripheral enhancement in the left lower scapula (arrow). B: May-Giemsa staining of cytological specimens from a bursitis-like lesion (magnification 400×). C: Anti-CD38 staining of cytological specimens from a bursitis-like lesion (magnification 400×).

fluid was aspirated. The fluid showed a white blood cell count of  $0.1 \times 10^9/L$  with 17% plasma cells, which were positive for CD38 on immunohistochemical staining (Fig. 3B and C). The patient received an additional four cycles of BD therapy without a further exacerbation of the plasmacytoma. The results of a physical examination before transplantation were unremarkable. His serum IgG level de-

creased to 599 mg/dL; IgG- $\lambda$  type M protein was still detected on serum immunoelectrophoresis. The serum free light chain ratio was within the normal limits at 0.81 (normal range: 0.26-1.65). His response before transplantation was classified as a PR. Subsequently, high-dose melphalan ( $100 \text{ mg/m}^2$  for 2 days) was administered followed by auto-HSCT; no severe adverse events were observed. IgG- $\lambda$  type



**Figure 4.** The clinical course before and after autologous hematopoietic stem cell transplantation. Immunoglobulin G (IgG) levels and the free light chain ( $\kappa/\lambda$ ) ratio, the results of immunoelectrophoresis, and immunofixation electrophoresis throughout the clinical course are shown. BD: bortezomib and dexamethasone, HD-Mel: high dose-melphalan, auto-HSCT: autologous hematopoietic stem cell transplantation, IEP: immunoelectrophoresis, IFE: immunofixation electrophoresis, D: detected, N/D: not detected

M protein was still detected by immunoelectrophoresis after auto-HSCT. Thus, his response after auto-HSCT was classified as a PR.

He was treated with bortezomib (1.0 mg/m<sup>2</sup> once in a 2 week cycle by subcutaneous infusion) as post-transplant maintenance therapy starting at 3 months after auto-HSCT. At 2 years after auto-HSCT, IgG- $\lambda$  type M protein was no longer detected by immunofixation electrophoresis and the serum free light chain ratio was within the normal range. PET/CT showed no abnormal accumulation of <sup>18</sup>F-FDG (data not shown). Thereafter, bortezomib was administered once a month for another year. At 3 years after auto-HSCT, IgG- $\lambda$  type M protein was not detected by immunofixation electrophoresis and the serum free light chain ratio was within normal limits (Fig. 4). In the maintenance phase, he experienced grade 1 taste alteration and grade 1 peripheral sensory neuropathy as adverse events. Consequently, bortezomib treatment was stopped and an sCR has been maintained without recurrence for 8 months.

## Discussion

We report a case of relapsed MSP. The expression of CD138 was low and 17p deletion was detected. The patient

received BD induction therapy and high-dose melphalan followed by auto-HSCT. Biweekly bortezomib maintenance therapy was started at 3 months after transplantation, and an sCR was achieved and maintained.

SBP tends to progress to MM at a rate of 65-84% in 10 years (1). The present patient did not progress to MM but experienced a relapse of MSP. There are few organized reports describing the risk factors for progression to multiple plasmacytomas. In patients with MM, 17p deletion is relatively rare at the time of the diagnosis, whereas its incidence increases with disease progression (11). The presence of 17p deletion is associated with a significantly shorter overall survival in myeloma patients. In the era of conventional chemotherapy, the median overall survival in patients with and without 17p deletion is reported to be 13.9 months and 38.7 months, respectively (12). Bortezomib-based induction therapy has not improved the outcome of MM patients with 17p deletion (13). However, the prognosis of plasmacytoma patients with 17p deletion remains unclear. In the present case, the presence or absence of 17p deletion could not be determined at the initial diagnosis or at the time of the first relapse, but was detected at the second relapse. Since the second relapse occurred in a short period of time, 17p deletion was presumed to have emerged between the first and second



relapse.

An analysis of the plasmacytoma of the present patient at both the first and second relapse showed that the level of CD138 expression was low. CD138 is a characteristic marker of plasma and myeloma cells. CD138 mediates the adhesion of myeloma cells to the bone marrow stromal matrix (14). In the present case, we hypothesized that the SBP progressed to multiple plasmacytomas with an unusual manifestation of a bursitis-like lesion because of the low expression of CD138. Pre-plasma cells (CD19<sup>+</sup>CD138<sup>+</sup>) similar to the cell surface phenotype observed at the first relapse of the present case show drug resistance that is up to 300-fold higher than that of the CD19<sup>+</sup>CD138<sup>+</sup> plasma cell population (7). In the present case, flow cytometry of tumor cells from lymph nodes at the second relapse revealed CD19<sup>+</sup>CD138<sup>low</sup> cells, which show immature characteristics after they acquire the expression of CD19. Although the presence and characterization of MM stem cells or myeloma-initiating cells has been controversial, several laboratories have identified peripheral blood clonal CD19<sup>+</sup> cells, which may be MM stem cells or the tumor-propagating cell responsible for relapse (15-17). In the present patient, the CD19<sup>+</sup> cells that persisted after the resection of the SBP at the time of the first relapse might have proliferated in the form of multiple plasmacytomas. Furthermore, the expression of CD19 in MM cells has been associated with shorter progression free and overall survival (18, 19). Inoue et al. reported the clinical significance of decreased CD138 expression in MM. A decrease in CD138<sup>+</sup> levels is associated with a poor prognosis, even during the course of treatment (20).

Recent reports show that the administration of bortezomib before and after transplantation improves overall and progression-free survival in MM patients with 17p deletion. Long-term maintenance therapy with bortezomib after transplantation is recommended for MM patients with 17p deletion (21). The low expression of CD138 and 17p deletion predicted a poor prognosis in the present patient. Hence, we decided to perform auto-HSCT and to administer post-transplantation bortezomib maintenance therapy for a long period. An sCR was achieved without recurrence despite the presence of 17p deletion. Bortezomib protects p53 from degradation and promotes apoptosis (22). Although the FISH analysis showed the deletion of 17p, bortezomib may have induced p53-independent apoptosis in the present case (23). Lenalidomide was another treatment option for maintenance therapy after transplantation in the patient at that time. However, *in vitro* experiments indicate that CD138-low myeloma cells may be resistant to lenalidomide (8). Moreover, lenalidomide is not effective in overcoming the poor prognosis of MM in patients with 17p deletion (24). A new agent, carfilzomib monotherapy, does not improve the overall survival of patients with 17p deletion (25).

In the present study, we reported the case of a patient with relapsed MSP in whom an sCR was successfully

achieved after auto-HSCT followed by bortezomib maintenance despite the presence of poor prognostic factors. Auto-HSCT followed by bortezomib maintenance therapy is tolerable, and a deep response may improve the outcome of patients with relapsed plasmacytoma with poor prognostic factors. It is important to clarify the risk classification of plasmacytoma. Further clinical studies are needed to establish a suitable treatment strategy for multiple plasmacytomas.

#### Author's disclosure of potential Conflicts of Interest (COI).

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