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Case Report

A case of secondary plasma cell leukemia resistant to novel agents, in which stringent complete remission was achieved and maintained for a long period of time after VAD therapy and tandem autologous transplantation

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Abstract: A 61-year-old woman was diagnosed in June 2011 as having immunoglobulin G (IgG) κ-type multiple myeloma (MM), stage II, according to the International Staging System (ISS). Chromosome analysis showed a complex karyotype, including t(11;14) and del 13q. Analysis of the cell surface markers revealed that the cells were positive for mature plasma cell-1 (MPC-1), and negative for cluster of differentiation (CD) 45 and CD49e, suggestive of an intermediate level of maturity of the cells. The disease was refractory to bortezomib-dexamethasone (BD) therapy and progressed to plasma cell leukemia despite the treatment. Treatment was therefore switched to lenalidomide-dexamethasone (RD) therapy, however, the condition again proved to be refractory to this therapy. A partial response (PR) was achieved with vincristine-doxorubicin-dexamethasone (VAD) therapy. The residual plasma cells became CD45-positive, suggesting a change of the cells from an intermediate level of maturity to mature cells. In December, autologous peripheral blood stem cell transplantation (Auto-PBSCT) was performed after high-dose melphalan therapy (melphalan 200 mg/m^2) as pretreatment. PR was observed and a second Auto-PBSCT was performed in July 2012. Stringent complete remission (sCR) has been maintained for 2 years since, without any further treatment. This is the first reported case of secondary plasma cell leukemia (sPCL) resistant to new drugs that was successfully treated by high-dose melphalan in combination with VAD therapy and Auto-PBSCT.

Keywords: Bortezomib, lenalidomide, VAD therapy, high-dose chemotherapy in combination with autologous peripheral blood stem cell transplantation

Introduction

Plasma cell leukemia (PCL) is a condition characterized by a plasma cell count of 2000/μL or more and/or a plasma cell percentage of 20% or higher in the differential white blood cell count in the peripheral blood [1, 2]. PCL is rare, accounting for approximately 1% to 2% of all plasma cell tumors, and can be classified into primary and secondary PCL (pPCL and sPCL). pPCL refers to PCL, a leukemic state of the plasma cells, that develops *de novo*, in the absence of a history of multiple myeloma (MM), while sPCL refers to leukemic transformation of plasma cells occurring in patients with a history of MM; sPCL is considered to be a terminal condition, and pPCL and sPCL are considered to account for approximately 60% and 40% of all cases of PCL [1, 2].

The median survival time of patient with MM is 44.8 months [3]. The prognosis of pPCL is generally poor, with median survival times varying among reports from 2 to 45 months [4-9]. The prognosis of sPCL is worse, with a reported median survival time of 1.3 to 19 months [8, 9].

Table 1. Laboratory findings at admission

Peripheral blood	WBC	5800/mL
	Band	7.0%
	Seg	41.0%
	Ly	50.0% ↑
	Mono	1.5% ↓
	Eo	1.5%
	RBC	265 × 10^4/mL ↓
	Hb	8.7 g/dL ↓
	Ht	26.9% ↓
	MCV	101.5 fl ↑
	MCH	32.8 pg
	Plt	19.2 × 10^4/mL
	Reti	1.7%
Blood coagulation profile	PT	81.0%
	APTT	34.0 sec
	Fbg	421.0 mg/dL ↑
	FDP	£5 mg/mL
Urinalysis	pH	6.0
	Specific gravity	1.020
	Protein	30 mg/dL ↑
	Occult blood	3+ ↑
Biochemistry	T.P	10.3 g/dL ↑
	Alb	2.6 g/dL ↓
	AST	34 IU/L
	ALT	37 IU/L
	LDH	269 IU/L ↑
	ALP	237 IU/L
	g-GTP	29 IU/L
	T-Bil	0.49 mg/dL
	BUN	21 mg/dL
	Cr	0.41 mg/dL ↓
	Uric acid	4.3 mg/dL
	CRP	0.1 mg/dL
	Ferritin	457 ng/mL ↑
Immunoserological findings	IgG	6384 mg/dL ↑
	IgA	8 mg/dL ↓
	IgM	12 mg/dL ↓
	IgD	0.6 mg/dL ↓
	Serum b2-MG	3.0 mg/dL ↑
	IEP (specific antiserum)	IgG-k positive
	IEP (urinary BJP)	BJP-k positive
Bone marrow smear findings	Nucleated cell count	70.5 × 10^4/mL ↑
	Megakaryocyte count	72/mL
	Plasma cells	76.4% ↑
Flow cytometry of bone marrow blood	CD19	1.3%
	CD20	14.5%
	CD45	4.2%
	CD49e	2.7%

This is considered to be because the incidence of poor prognostic chromosomal abnormalities, such as the amplification of t(4;14), t(14;16), del(17p), del(13q), del(1p21), 1q21 and MYC translocation or amplification, is higher than that in MM [5]; the present patient had del(13q). In addition, it has also been pointed out that a reduction in the activity of p53 causes sPCL [9]. Patients with sPCL have a higher incidence of bone lesions, but a lower incidence of extramedullary infiltration and renal disorder, as compared to those with pPCL [5]. The high incidence of bone lesions may also exert an influence on the prognosis in patients with sPCL; our present patient also had bone lesions.

There is no established standard treatment for PCL. New drugs can be expected to have a lower degree of efficacy against PCL than against MM. This study reports that the use of conventional chemotherapy (high-dose melphalan therapy in combination with vincristine-doxorubicin-dexamethasone (VAD) therapy and autologous peripheral blood stem cell transplantation (AutoPBSCT)) was extremely useful in a patient with sPCL in whom the disease was refractory to the new drugs.

Case report

A 61-year-old woman complained of low back

	CD52	6.9%
	CD54	24.3% ↑
	CD56	97.3% ↑
	CD126	1.8%
	CD138	59.7% ↑
	MPC-1	56.6% ↑
	κ	88.7% ↑
	λ	0.2%
Bone marrow blood chromosome (G-banding)	46,XX,-2,add(8)(q24),t(11;14 (q13;q32),del(13)(q?),der(16)t(1;16 (q21;q13),+mar1 2/18 46,XX 16/18	

WBC, white blood cell; Band, banding; Seg, segment; Ly, lymphocyte; Mono, monocyte; Eo, eosinophil; RBC, red blood cells; Hb, hemoglobin; Ht, hematocrit; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; Plt, platelet; Reti, reticulocyte, PT, prothrombin time; APTT, activated partial thromboplastin time; Fbg, fibrinogen; FDP, fibrin fibrinogen degradation product; pH, hydrogen ion concentration; T.P, total protein; Alb, albumin; AST, aspartate aminotransferase;a lanine aminotransferase; LDH, lactate dehydrogenase; ALP, alkaline phosphatase; GTP, glutamyl transpeptidase; T-Bil, total bilirubin; BUN, blood urea nitrogen; Cr, creatinine; CRP, C-reactive protein C; MG, microglobulin; IEP, immunoelectrophoresis; BJP, bence jones protein.

pain and numbness in the lower extremity extending from the left buttock to the left thigh. Her medical history included surgery for pneumothorax and uterine myoma at age 40, surgery for cervical spine and rib fractures at age 42, initiation of insulin for type II diabetes at age 58, cellulitis of the right thigh at age 60, and lumbar spinal canal stenosis at age 61. There was no significant family history. She visited a local hospital with the aforementioned complaints of back pain and numbness of the lower extremity in June 2011. With a suspected diagnosis of MM, based on the detection of hyperproteinemia (10.3 g/dL) and elevated immunoglobulin G (IgG) levels (6384 mg/dL), the patient was admitted to our department in July 2011.

Examination at admission revealed that the patient was 145.0 cm tall and weighed 41.9 kg; the body temperature was 36.3°C, the blood pressure 108/70 mmHg, and the pulse 66/minute, regular; the patient was fully conscious, conjunctival pallor was present, however, there was no icteric conjunctivae, superficial lymphadenopathy or hepatosplenomegaly; neurological examination for the low back pain and numbness extending from the left buttock to the left thigh revealed mildly exaggerated deep tendon reflexes in both lower extremities and no abnormal results of manual muscle testing.

Laboratory findings at admission (**Table 1**) included anemia, hyperproteinemia, elevated IgG levels, and proteinuria. Immunoelectrophoresis (IEP) revealed IgG-κ in the serum and Bence Jones protein (BJP)-κ in the urine. The serum albumin level was 2.6 g/dL and the serum β2-microglobulin level was 3.0 mg/dL. Bone marrow examination revealed that 76.4% of the cells comprised somewhat hyperplastic plasma cells with a somewhat high nucleus-cytoplasm (N/C) ratio (**Figure 1A** and **1B**). Flow cytometry revealed that the cells were positive for cluster of differentiation (CD) 138, mature plasma cell-1 (MPC-1) and cytoplasmic κ expression, but negative for CD45, CD49e and CD20 expression (**Figure 2A-D**). Chromosome G-banding analysis revealed a complex karyotype, including t(11;14) and del 13q (**Table 1**). On magnetic resonance imaging (MRI), both T1- and T2-weighted images showed a number of low-signal areas in the cervical to the lumbar spine that were enhanced by contrast (**Figure 3A-C**). In addition, computed tomography (CT) showed a bilateral paravertebral mass extending from the mid to lower thoracic spine (**Figure 3D**). Based on these findings, the patient was diagnosed as having IgG-κ type MM, stage IIIA according to the Durie and Salmon classification, and stage II disease according to the International Staging System (ISS). Positivity for MPC-1 and negativity for CD45 and CD49e (**Figure 2B** and **2C**) suggested an intermediate level of maturity of the plasma cells.

Her clinical course after admission is shown in **Figure 4**. Bortezomib-dexamethasone (BD) therapy (intravenous injection of bortezomib at 1.3 mg/m^2 on days 1, 8, 15 and 22, drug withdrawal for 7 days, and oral administration of 20 mg/day of dexamethasone on days 1, 2, 8, 9, 15, 16, 22 and 23, each treatment cycle lasting for 5 Weeks) was started in July. In addition, zoledronic acid hydrate was also administered once a month. After 3 courses of BD therapy, however, the disease progressed to sPCL (plasma cell count in the peripheral blood, 2050/

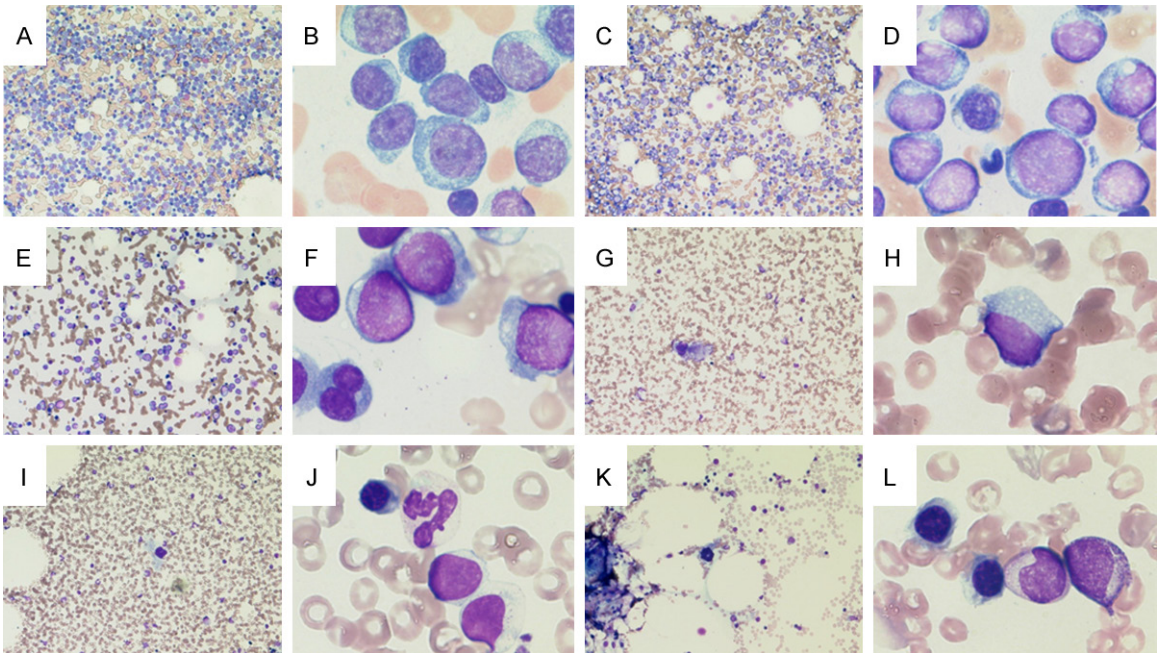

Figure 1. Bone marrow smear (Wright-Giemsa staining). A. A marked increase in the percentage of plasma cells was seen before the start of treatment (× 100). B. A marked increase in relatively immature plasma cells with a high N/C ratio was seen before the start of treatment (× 1000). C. No significant decrease in plasma cell count was observed after 3 courses of BD therapy (× 100). D. No therapeutic effect was evident, and in fact, the count of relatively immature plasma cells with a high N/C ratio increased after 3 courses of BD therapy (× 1000). E. No decrease in the plasma cells was observed after one course of RD therapy (× 100). F. No significant decrease in the number of relatively immature plasma cells with high N/C ratios was observed after one course of RD therapy (× 1000). G. Marked decrease in the number of plasma cells was observed after one course of VAD therapy. Megakaryocytes became apparent (× 100). H. Increase in the maturity level of the residual plasma cells with a decreased N/C ratio after one course of VAD therapy (×1000). I. No increase in the number of plasma cells was observed by 3 months after the first Auto-PBSCT (× 100). J. The plasma cell percentage began to decrease by 3 months after the first Auto-PBSCT (× 1000). K. Scarcely any increase of the plasma cell percentage was observed at 3 months after the second Auto-PBSCT (× 100). L. Scarcely any increase of the plasma cell percentage was observed at 3 months after the second Auto-PBSCT (× 1000).

μL). There was no decrease of the M-protein or the percentage of plasma cells in the bone marrow (62.6%) (**Figures 1C**, **1D** and **2E-H**). The therapy was therefore switched to lenalidomide-dexamethasone (RD) therapy (oral administration of 25 mg/day of lenalidomide on days 1 to 21, drug withdrawal for 7 days, and oral administration of 40 mg/day of dexamethasone on days 1, 8, 15, and 22, each treatment cycle lasting for 4 weeks) in September. The peripheral blood plasma cell count temporarily decreased to 22 cells/μL immediately after the start of RD therapy, but increased to 82 cells/μL immediately after completion of the first course. Also in the bone marrow, the proportion of plasma cells increased to 78.4% (**Figures 1E**, **1F** and **2I-L**). Therefore, we judged that the disease was resistant to the new drugs. VAD therapy (0.4 mg/body of vincristine on days 1 to 4, 10 mg/m^2 of doxorubicin on days 1 to 4, and 40 mg/body of dexamethasone on days 1 to 4, 9 to 12 and 17 to 20), which is the conventional chemotherapy, was started in October. During the first course of VAD therapy, the plasma cells rapidly disappeared from the peripheral blood and the serum IgG level decreased to 2403 mg/dL. The percentage of plasma cells in the bone marrow decreased to 1.6% (**Figure 1G** and **1H**). Chromosome analysis showed a normal karyotype. In addition, the residual plasma cells had a low N/C ratio (**Figure 1H**), and flow cytometry showed that the plasma cells that were CD138-positive, cytoplasmic κ-positive, MPC-1-positive were also positive for CD45 and CD20, suggesting a change of the cells from an intermediate level of maturity to mature cells (**Figure 2M-P**). IEP showed a positive result, indicating partial response (PR). At this time, the patient was in a depressed state, and she and her family wished for the treat-

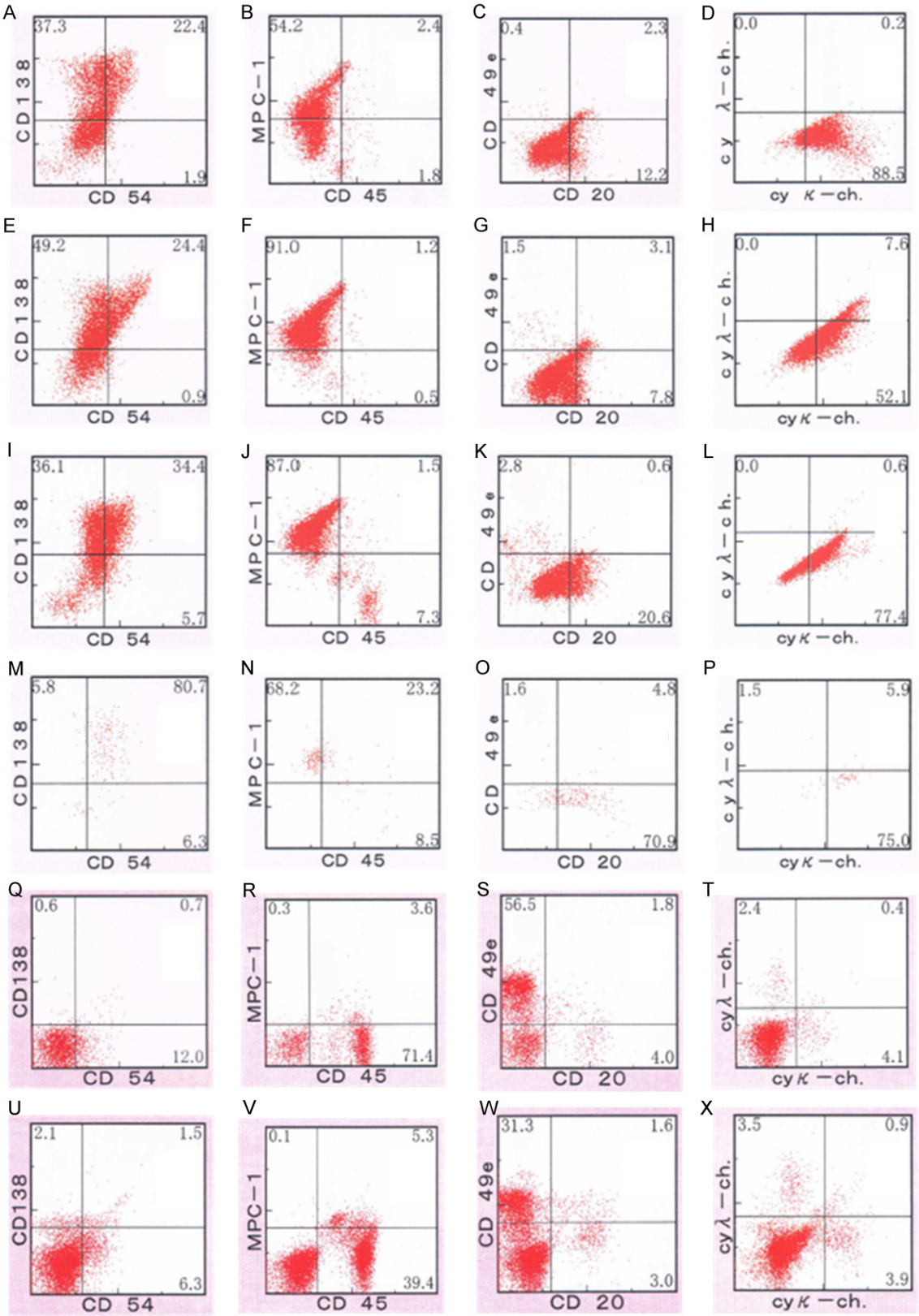

Figure 2. Flow cytometry of bone marrow blood (analysis in the CD38-positive cell gate). A-D. Before treatment, the cells were positive for CD138, MPC-1 and cytoplasmic κ, and negative for CD45 and CD49e, suggestive of an intermediate level of maturity of the cells. E-H. A similar pattern was observed after BD therapy, suggestive of an

intermediate level of maturity of the cells. I-L. After RD therapy, some cells became positive for CD45 and some became positive for CD20, suggesting that at least some of the cells were mature. M-P. After VAD therapy, some cells became positive for CD45 and most cells became positive for CD20, although the overall number of cells was small. In addition, the proportion of mature plasma cells increased, although the cells remained positive for cytoplasmic κ. Q-S. Three months after the first Auto-PBSCT, there were no CD138-positive, cytoplasmic κ-positive plasma cells. U-W. Three months after the second Auto-PBSCT, no CD138-positive, cytoplasmic κ-positive plasma cells were seen.

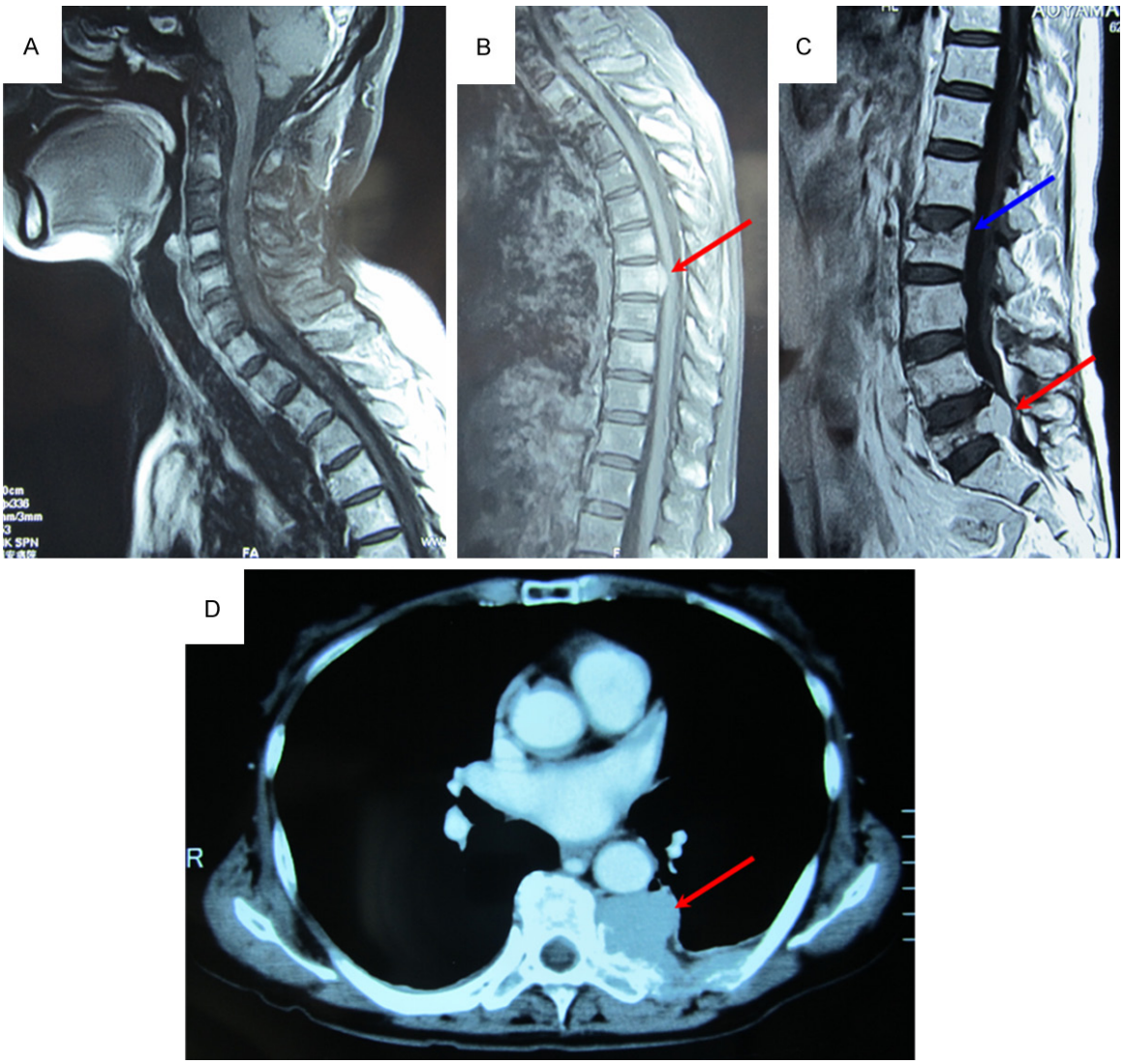

Figure 3. Imaging findings. A. Contrast-enhanced MRI of the cervical spine revealed many spotty signals in the cervical spine vertebral bodies, which were enhanced by gadolinium. B. Contrast-enhanced MRI of the thoracic spine revealed many spotty signals in the vertebral bodies of the thoracic spine, which were enhanced by gadolinium. Compression of the dural sac by an extraosseous lesion was observed (red arrow), suggestive of a plasmacytoma. C. Contrast-enhanced MRI of the lumbar spine revealed many spotty signals in the vertebral bodies of the lumbar spine, which were enhanced by gadolinium. There were compression fractures in L2 and L5 (blue arrow) and a soft tissue mass at L5 (red arrow), suggestive of a plasmacytoma. D. Contrast-enhanced chest CT revealed a soft tissue mass in the dorsal thoracic aorta (red arrow), suggestive of a plasmacytoma.

ment to be terminated early and for the patient to be discharged from the hospital. Therefore, the VAD therapy was discontinued after the first course. Concomitant use of high-dose cyclophosphamide therapy (intravenous injection of 2000 mg/m^2 of cyclophosphamide on days 1 and 2) and granulocyte colony-stimulating factor was started in November and autologous

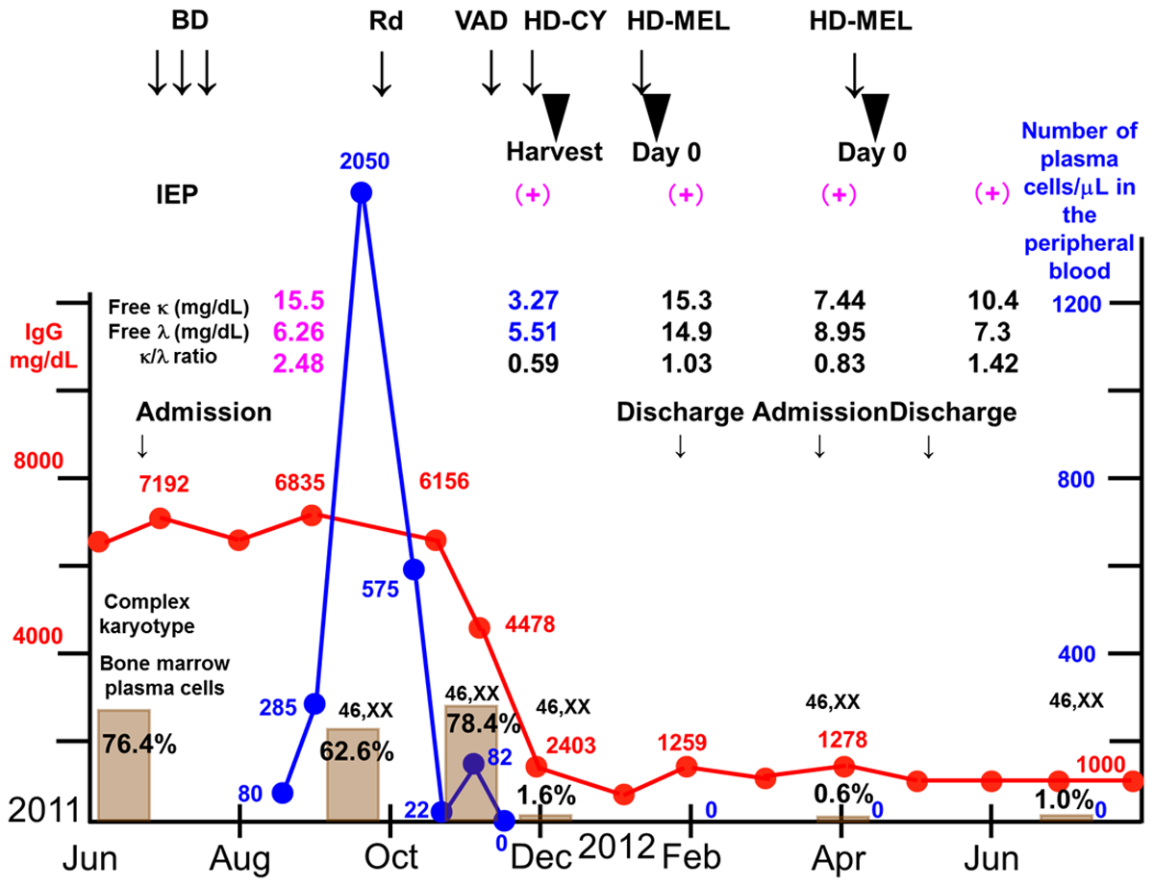

Figure 4. Clinical course. The disease progressed to sPCL after the third course of BD therapy; therefore, the therapy was switched to RD therapy, however, the patient did not respond to RD therapy either. VAD therapy was started, and PR was obtained. Tandem Auto-PBSCT was performed, which led to sCR 8 months later. The sCR has been maintained for 2 years after the tandem Auto-PBSCT. HD-CY, high-dose cyclophosphamide; HD-MEL, high dose melphalan.

peripheral blood stem cells were collected in December (CD34 positive: 4.0 × 10^6 cells/kg). Auto-PBSCT was performed after high-dose melphalan therapy (melphalan 200 mg/m^2) as pretreatment. Engraftment was confirmed on day 10, and the patient was discharged in January 2012. Bone marrow examination showed no increase in the percentage of plasma cells until April, 3 months after the transplantation (**Figure 1I** and **1J**). Flow cytometry revealed that the cells became negative for CD138, MPC-1, CD20 and cytoplasmic κ (**Figure 2Q-T**), but positive for CD45 and CD49e. However, IEP showed a positive result, indicating PR. In the same month, therefore, a second Auto-PBSCT was performed. In July, 3 months after the second transplantation, bone marrow examination showed no increase in the percentage of plasma cells (**Figure 1K** and **1L**) and flow cytometry showed that the cells were negative for CD138, MPC-1, CD20 and cytoplasmic κ, and positive for CD45 and CD49e (**Figure 2U-X**), like in the earlier examination. However, IEP and immunofixation electrophoresis (IFP) showed a positive result, indicating PR. Because the patient did not wish to receive consolidation or maintenance therapy, she was followed up without further treatment. In December 2012, 8 months after the second Auto-PBSCT, the IFP showed a negative result. The serum free light chain (FLC) κ/λ ratio was also within the reference range (free κ, 8.1 mg/L; free λ, 9.6 mg/L; κ/λ ratio, 0.84), leading to a diagnosis of stringent complete remission (sCR). As of May 2014, the sCR had been maintained for 2 years after the second transplantation.

Discussion

We encountered a patient with sPCL resistant to BD and RD therapy, who was successfully

Table 2. Cases of sPCL treated by VAD therapy and autologous transplantation

Case	Age/ sex	MM type	Chromo-some	Treatment of MM	Interval to leukemic transformation	Treatment of leuke-mic transformation	Effi-cacy	Additional treatment	Outcome	Refer-ence
1	40/M	n.a	n.a	n.a	n.a	VAD × 4/ASCT	n.a.	None	Survival for 0.3 m F/U loss	17
2	37/M	n.a	n.a	n.a	n.a	VAD × 3/ASCT	None	None	Death 0.2 m later	17
3	44/M	n.a	n.a	n.a	n.a	CHOP × 1/VAD × 3/ ASCT/I.T. × 2/TD	None	None	Death 1.3 m later	17
4	61/F	IgG/k	Complex karyotype	BD/RD	3 M	VAD × 1/tandem ASCT	sCR	None	Survival for 2 y with sCR	This case

M, male; F, female; n.a, not available; VAD, vincristine, doxorubicin, dexamethasone; ASCT, autologus stem cell transplantation; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisolone; I.T., intrathecal methotrexate; TD, thalidomide, dexamethasone; sCR, stingent complete remission; m, month; F/U, follow-up; y, year.

treated by VAD therapy, with sCR achieved and maintained for a long period of time after tandem Auto-PBSCT alone (without consolidation and maintenance therapy). This case was considered to be valuable for investigating the treatment options for sPCL.

To the best of our knowledge, there have been approximately 138 reported cases of sPCL [4, 6, 8-23]. Because sPCL is a rare disease, no prospective clinical trials have been conducted and there have been only case reports and retrospective studies involving small numbers of patients.

There have been only 4 reported cases, including the present one, of sPCL treated with the combination of VAD therapy and Auto-PBSCT (**Table 2**). The outcome was unknown in one of the patients, and 2 patients died early. Of the 4, only the patient reported here has survived for a long period of time. No differences were apparent between the patients who died early and the present patient, and the reason for the long-term survival remains unknown. However, in the patient reported herein, the residual plasma cells after VAD therapy became CD45-positive (**Figure 2J** and **2N**), suggesting differentiation of the cells from an intermediate level of maturity to fully mature cells. Our results suggested that with this change in the degree of maturity of the cells, the patient became more sensitive to conventional chemotherapy, particularly doxorubicin, and that the subsequent Auto-PBSCT became effective following this change. It is considered necessary to periodically examine the cell maturity by flow cytometry for assessing the efficacy of chemotherapy.

In addition, although VAD was shown to be effective in one of the previously reported cases [19], as in the present case, it has also been reported that VAD alone is, in general, ineffective [9, 20, 23]. Furthermore, many studies have reported that standard chemotherapy regimens for MM not containing the new drugs resulted in poor outcomes [5, 7]. From the above, it is considered necessary to make quick judgments about the patient's disease stage and to perform careful follow-up, because sPCL is rapidly progressive and has an extremely poor prognosis.

Moreover, Auto-PBSCT has not been shown to be effective in studies other than the present one. It is considered necessary to accumulate a larger number of cases and to comparatively investigate the characteristics of patients treated successfully and unsuccessfully by Auto-PBSCT.

While a number of studies have demonstrated the efficacy of bortezomib [4, 6, 7, 12, 16, 18, 21], one study has reported the efficacy of lenalidomide [14]. Some studies have reported the effectiveness of thalidomide [22, 23], while others have reported that thalidomide is ineffective [13, 22].

Allotransplantation has also been reported to be effective [6]. All of these studies involved only small numbers of patients, and it is necessary to accumulate a larger number of cases for investigation in the future.

The combination of VAD therapy and Auto-PBSCT is considered to be one of the valid treatment options for sPCL resistant to new drugs, like the present case.

Disclosure of conflict of interest

None.

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