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Case Study

A Case of Extramedullary Plasmablastic Plasmacytoma Successfully Treated Using a Combination of Thalidomide and Dexamethasone and a Review of the Medical Literature

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A 56-year-old man developed epistaxis, hoarseness, and swelling of a finger in March 2010. On the basis of biopsies of the masses in the pharynx and finger, he was diagnosed with extramedullary plasmablastic plasmacytoma, with somewhat immature $CD45^+$, MPC-1^-, and $CD49e^-$. CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone) and VCAP (vincristine, cyclophosphamide, doxorubicin, and prednisolone) therapy was ineffective, but combination therapy with thalidomide and dexamethasone was highly effective. Thalidomide monotherapy successfully maintained partial remission for approximately 7 months. A mass appeared in the right neck in February 2011, and a biopsy confirmed recurrence. Changes to CD45 negativity and MPC-1 partial positivity were seen, while CD49e negativity persisted, suggesting that the plasmablastic plasmacytoma had reverted to a more immature state. Bortezomib therapy was started in March 2011 and was effective. However, during the second round of treatment, the patient developed acute lung injury, which was improved by steroid pulse therapy. After the discontinuation of bortezomib, the extramedullary mass increased rapidly, and the patient died of multiple organ failure. An autopsy showed that plasmablastic plasmacytomas had infiltrated into multiple organs. Extramedullary plasmacytomas and those that revert to an immature state are associated with a poor prognosis, so further treatment improvements are needed in the future. 〔*J Clin Exp Hematop 53(1): 21-28, 2013*〕

Keywords: thalidomide, plasmablastic plasmacytoma, extramedullary plasmacytoma, MPC-1, CD45

INTRODUCTION

The immunophenotypes of CD45, MPC-1, and CD49e are useful for identifying the degree of differentiation in plasmacytomas.[1] Generally, $CD45^+$, MPC-1^+, and $CD49e^+$ plasmacytomas are considered to be mature; $CD45^-$, MPC-1^-, and $CD49e^-$ plasmacytomas are considered to be immature; and all others are considered to be intermediate forms. Plasmablastic plasmacytoma has a poor prognosis with a median survival time of approximately 10 months,[2] and thalidomide is considered to be poorly effective for plasmablastic plasmacytoma.[3-5] In addition, approximately 15% to 20% of patients with multiple myeloma have extramedullary plasmacytoma at the time of diagnosis, and 15% of all patients with multiple myeloma develop chemotherapy-resistant extramedullary plasmacytoma during the course of their disease, resulting in a poor prognosis.[6] In patients in whom extramedullary plasmacytoma has been reported to be successfully treated with thalidomide, the duration of the effect was temporary (6.2 months). In the present case as well, thalidomide was only effective for approximately 7 months. The reversion of the plasmablastic plasmacytoma to an immature state was speculated to be one of the causes of this, as CD45 negativity occurred. New treatment strategies, such as polypharmacy, are urgently needed.

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CASE REPORT

A 56-year-old man complained of epistaxis, hoarseness, and swelling of the tip of the fourth finger of the left hand. In his medical history, he had undergone coronary artery bypass grafting for angina and had developed atrial fibrillation, hypertension, and hyperlipidemia in 2002. In the history of his present illness, the patient had developed various complaints

and had visited the Department of Otolaryngology of our hospital in March 2010. In May 2010, a magnetic resonance imaging examination showed a 2 × 2 × 3-cm-sized mass lesion between the left wall of the nasopharynx and the sphenoid sinus (Fig. 1a), and the patient was admitted to the Department of Otolaryngology of our hospital.

At the time of admission, the patient exhibited somnolence, anemic bulbar conjunctiva, a temperature of 38°C, blood pressure of 92/64 mmHg, and, because of atrial fibrillation, an irregular pulse of 92 beats per minute. The hepatic, splenic, and superficial lymph nodes were not palpable. His performance status was poor (score 4). The laboratory findings at the time of his admission are shown in Table 1. The IgG and IgA values were elevated. A mass lesion was seen in the liver (Fig. 1b) and necrosis was observed at the tip of the fourth finger of the left hand (Fig. 1c). An X-ray examination showed osteolysis (Fig. 1d). A pharyngeal mass biopsy revealed a plasmablastic plasmacytoma (Fig. 2a). Immunohistochemical staining showed immunoglobulin light-chain$^+$ with $\varkappa$ predominance (Fig. 2c), CD20$^-$ (Fig. 2e), IgG$^+$ (Fig. 2f), and Ki-67$^+$ at a high rate (Fig. 2h), and *in situ* hybridization of Epstein-Barr virus-encoded ribonucleic acid was negative (Fig. 2i). A flow cytometry examination revealed CD138$^+$, CD56$^+$, cytoplasmic κ^+, CD45$^+$, MPC-1$^-$, CD49e$^-$, and CD20$^-$ (Fig. 3a-3e). Chromosome G-banding was not clear because of the poor growth. Amputation of the tip of the fourth finger of the left hand was performed, and a finding of plasmablastic plasmacytoma was obtained, similar to the pharyngeal mass (Fig. 2b). On the basis of the above findings, the patient was diagnosed with IgG extramedullary plasmablastic plasmacytoma. The patient was categorized into stage III according to the International Staging System and into stage IIIB according to the Durie & Salmon system.

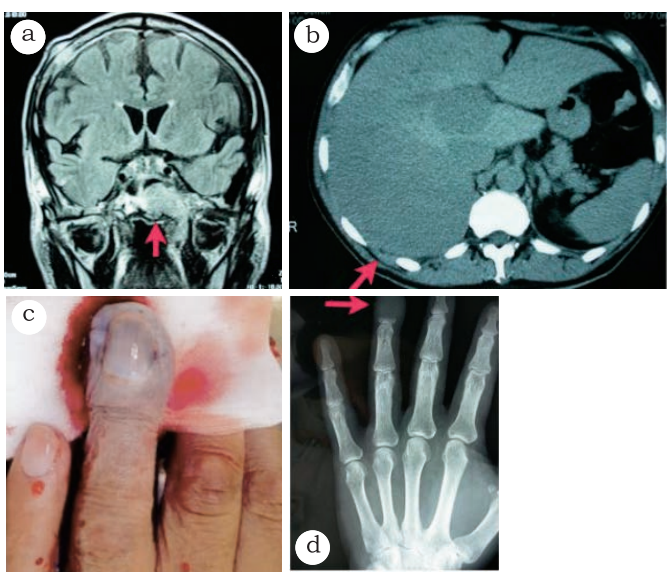

Fig. 1. Imaging findings. (***1a***) Magnetic resonance imaging of the head : a 2 × 2 × 3-cm-sized mass was noted between the left wall of the nasopharynx and the sphenoid sinus (←). (***1b***) Abdominal computed tomography : a 12-cm-sized mass was found in the right lobe of the liver (←), and a 6-cm-sized mass was found in the porta hepatis. A 2.5-cm-sized mass was found near the head of the pancreas (data not shown). (***1c***) Necrosis was observed at the tip of the fourth finger of the left hand (←). (***1d***) X-ray of the left hand showed osteolysis in the fourth finger distal to the distal interphalangeal joint (←).

The patient's clinical course after admission is shown in Fig. 4A. At first, it was very difficult to make the differential diagnosis between plasmablastic plasmacytoma and plasmablastic lymphoma, and because the patient's condition rapidly deteriorated before we were able to make a definite diagnosis, we started CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone) therapy in June 2010. However, this therapy was not sufficiently effective, and he received VCAP (vincristine, cyclophosphamide, doxorubicin, and prednisolone) therapy in July 2010. Although the IgG M-protein and serum β_2-microglobulin levels decreased, the serum lactate dehydrogenase level increased and the pharyngeal extramedullary mass became enlarged, suggesting that the plasma cells had reverted to an immature state. Echocardiography showed a decrease in the ejection fraction from 50% (before chemotherapy) to 30%, showing the exacerbation of heart failure. Since there was no increase in brightness on the echocardiogram, we ruled out cardiac amyloidosis. The patient received a combination of thalidomide and dexamethasone in August 2010. The patient showed a marked decrease in the size of the pharyngeal extramedullary mass (Fig. 5a-5d), a reduction in the serum lactate dehydrogenase level, and a further reduction in the IgG M-protein and serum β_2-microglobulin levels, indicating partial remission ; the patient was discharged in September 2010.

After discharge, the patient received maintenance therapy with thalidomide alone and his condition stabilized. In February 2011, subcutaneous masses appeared in the right neck and abdomen and increased rapidly. A computed tomography examination showed a decrease in the size of the mass in the left nasopharynx, but revealed a new mass in the right neck (Fig. 4b). Dexamethasone was concomitantly used, but the mass in the right neck increased. A biopsy of the mass was performed, and the patient was diagnosed with recurrence. The chromosomes (G-banding method) could not be fully characterized because of poor growth. The patient was readmitted to the hospital in March 2011 (Fig. 4a).

Thalidomide was discontinued, and the treatment was switched to the once-weekly administration of 0.7 mg/m^2 bortezomib. This dose was not effective, so it was increased to the twice-weekly administration of 1.3 mg/m^2. As a result, the extramedullary masses decreased rapidly. The patient developed acute lung injury after the second round of treatment. Invasive pulmonary aspergillosis was suspected on the

Table 1. Laboratory findings at the time of admission

Blood cell count		Biochemistry		Immunoelectrophoresis	
White blood cell	4,300/μL	Total bilirubin	1.8 mg/dL	Serum IgG-κ type	Positive
Neutrophil	57.3%	AST	35 IU/L	Urinary BJP-κ type	Positive
Lymphocyte	28.4%	ALT	12 IU/L	Urine test	
Monocyte	9.1%	LDH	371 IU/L	Protein	Negative
Eosinophil	1.8%	ALP	327 IU/L	Immune serum	
Basophil	0.7%	C-reactive protein	≤ 0.3 mg/dL	IgG	6,583 mg/dL
Hemoglobin	14.0%	β_2-microglobulin	9.6 mg/dL	IgA	1,507 mg/dL
Platelet	18.2×10^4/μL	Total protein	10.3 g/dL	IgM	144 mg/dL
Bone marrow		Albumin	2.5 g/dL	HTLV-1 antibody	(−)
Nucleated cell	2.9×10^4/μL	Blood nitrogen urea	20 mg/dL	HIV1/2 antibody	(−)
Megakaryocyte	≤ 15/ μL	Creatinine	1.15 mg/dL	HBs antigen	(−)
Blast	2.0%	Na	135 mM/L	HCV antibody	(−)
Plasma cell	1.2%	Cl	104 mM/L	Soluble IL-2 receptor	618 IU/L
Chromosome		K	4.1 mM/L	Electrocardiogram	
Chromosome (G-band)	46, XY	Ca (corrected)	13.7 mg/dL	Tachycardiac atrial fibrillation	
		Glucose	104 mg/dL		

AST, aspartate aminotransferase ; ALT, alanine transaminase ; LDH, lactate dehydrogenase ; ALP, alkaline phosphatase ; BJP, Bence-Jones protein ; HTLV-1, human T-cell leukemia virus-1 ; HIV1/2, human immunodeficiency virus 1/2 ; IL-2, interleukin-2

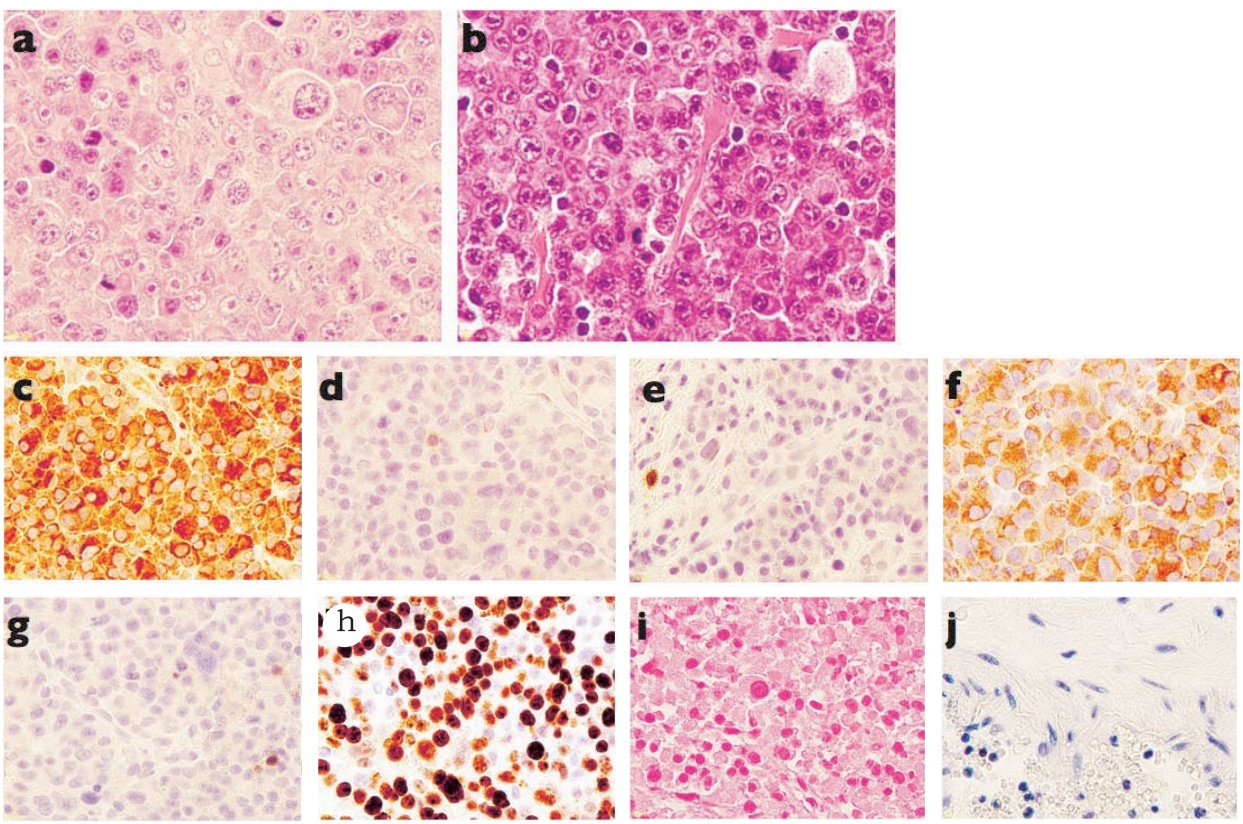

Fig. 2. Histological findings of the pharyngeal and left hand tumors, immunostaining and *in situ* hybridization of the pharyngeal tumor, and Congo red stain of the cardiac muscle. Both pharyngeal (*2a*) and left hand (*2b*) tumors contained somewhat large cells with maldistributed nuclei. Atypical plasmablastic plasmacytomas with a high nuclear/cytoplasmic ratio were visible. Tumor cells were immunoglobulin light-chain κ^+ (*2c*), immunoglobulin light-chain λ^- (*2d*), CD20$^-$ (*2e*), IgG$^+$ (*2f*), IgA$^-$ (*2g*), and had a high Ki-67 labeling index (*2h*). *In situ* hybridization of Epstein-Barr virus-encoded ribonucleic acid (*2i*) and Congo red stain (*2j*) were negative. (*2a*) & (*2b*) H&E stain, ×600. (*2c-2h*) counterstained with hematoxylin, ×600. (*2h* & *2j*) ×600.

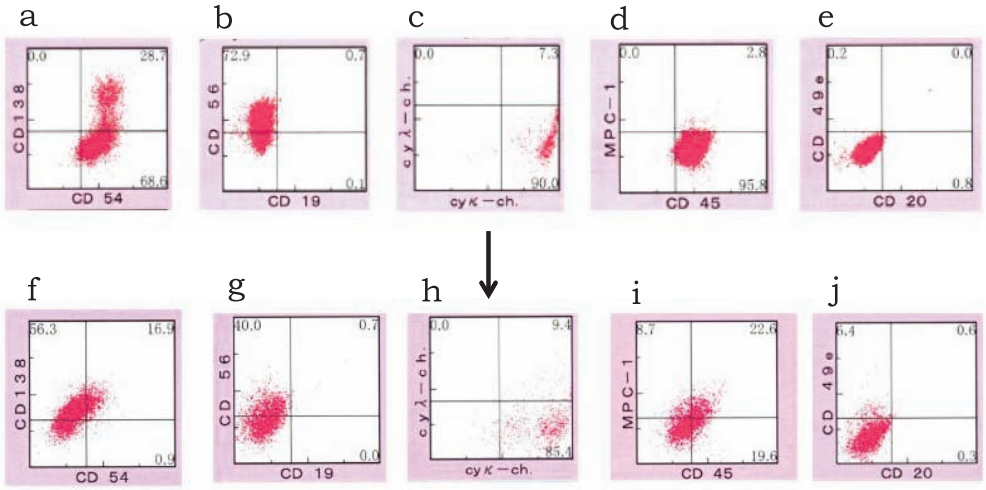

Fig. 3. Flow cytometry of the pharyngeal tumor with CD38 gating before (*3a-3e*) and after (*3f-3j*) the administration of thalidomide. Tumor cells were CD138^{+} in 28.7% (*3a*), CD56^{+} in 73.6% (*3b*), cytoplasmic κ^{+} in 90% (*3c*), MPC-1^{-} and CD45^{+} in 95.8%, MPC-1^{+} and CD45^{+} in 2.8% (*3d*), CD49e^{+} in 0.2% (*3e*), CD138^{+} in 73.2% (*3f*), CD56^{+} in 40.7% (*3g*), and cytoplasmic κ^{+} in 94.8% (*3h*). The proportion of MPC-1^{-} and CD45^{+} cells decreased to 19.6%, and that of MPC-1^{+} and CD45^{+} cells increased somewhat to 22.6% (*3i*). Tumor cells were also CD49e^{+} in 7% (*3j*).

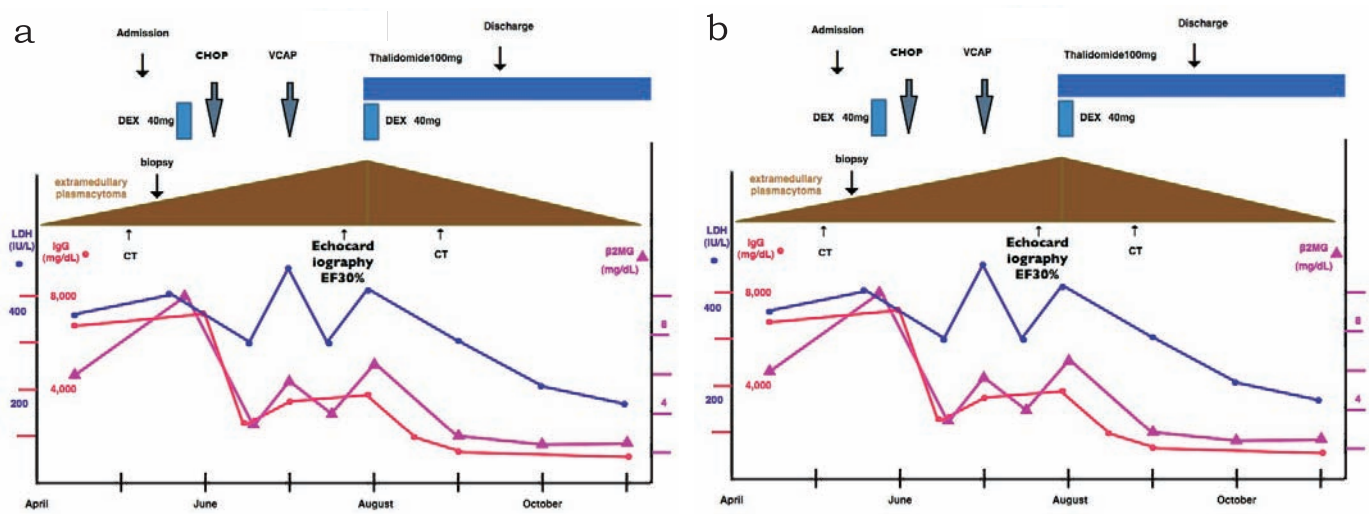

Fig. 4. Clinical course after the first (*4a*) and second (*4b*) admissions.

basis of serum aspergillus-antigen positivity, and liposomal amphotericin B was administered. However, no improvement was observed. On the basis of the clinical course and the computed tomography findings (Fig. 4b), the patient was diagnosed with acute lung injury because of the bortezomib treatment. Bortezomib was discontinued, and steroid pulse therapy with 1 g/day methylprednisolone for 3 days was performed. The lung lesions then improved rapidly, and the prednisolone dose was gradually reduced. After the discontinuation of bortezomib treatment, the extramedullary mass in the neck enlarged rapidly. After the prednisolone dose had been gradually reduced to 30 mg/day, acute lung injury recurred. Steroid pulse therapy was performed again, but the lung lesions deteriorated and the extramedullary mass also enlarged. The patient developed a mixed infection with *Candida*, *Cytomegalovirus*, and *Pseudomonas aeruginosa* and died as a result of multiple organ failure.

An autopsy showed a 10 × 7 × 3.5-cm-sized plasmablastic plasmacytoma that had infiltrated the submandibular gland between the right lower jaw and neck. Extramedullary infiltrations of 2.5-cm-sized, 1.2-cm-sized, and 1.1-cm-sized plasmablastic plasmacytomas were noted in the right lobe of the liver, under the visceral pleura of the right lung, and in bilateral adrenal glands, respectively. Findings indicating alveolar

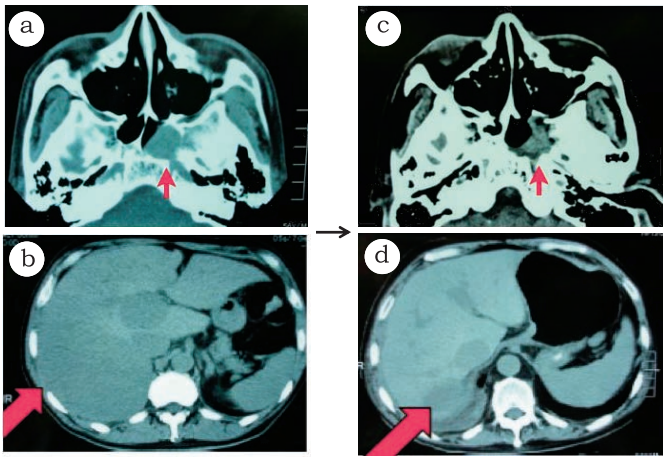

Fig. 5. Comparison of computed tomography findings before and after treatment with thalidomide. (***5a***) Before treatment with thalidomide, a mass between the left wall of the nasopharynx and the sphenoid sinus (←) was visible. (***5b***) Before treatment with thalidomide, a mass in the right lobe of the liver and a mass in the porta hepatis (←) were visible. (***5c & 5d***) After treatment with thalidomide, the masses decreased markedly in size (←).

pneumonia arising from a mixed infection and evidence of an old myocardial infarction were also seen. Myocardial Congo red staining was negative, and we ruled out amyloid (Fig. 2j). Although findings of fulminant hepatitis, possibly as a result of septic shock, were seen, no infiltration of tumor cells was seen. Both kidneys showed fibrous scarring, but no infiltration of tumor cells. The pancreas showed signs of atrophy, fibrosis, and inflammatory cell infiltration, but no infiltration of tumor cells. The spleen showed congestion, but no infiltration of tumor cells. The bone marrow was normal and showed no tumor cells. Brain dissection was not approved.

DISCUSSION AND CONCLUSIONS

This patient developed exacerbation of heart failure as well as atrial fibrillation and other symptoms after undergoing CHOP and VCAP therapy, and his performance status was 4. Therefore, bortezomib, which may have cardiotoxic effects, was not used as the first choice. In addition, lenalidomide could not be used, since it had not been approved in Japan at that time. Therefore, thalidomide was chosen and was temporarily effective.

Thalidomide alone is known to be effective for relapse/refractory myeloma with a response rate of 32% to 64%.[7,8] In addition, a synergistic effect with dexamethasone has also been reported.[9] Thalidomide reportedly has an antiangiogenic effect and exerts its antitumor effect by changing the microenvironment of the bone marrow in the presence of stromal cells.[10] Therefore, thalidomide is considered to be poorly effective for extramedullary masses.[4,5] However, thalidomide has been reported to have not only an antiangiogenic effect, but also to act directly on myeloma cells,[11] and from this perspective, thalidomide can be expected to have some effect on extramedullary masses.

In our literature search, thalidomide was reported to be effective for extramedullary plasmacytoma in 27 cases, including the present case (Table 2). However, only 2 cases, that is, the present case and case 7 reported by Nakasato *et al*. (shown in Table), were diagnosed as plasmablastic plasmacytoma after examining the level of maturity. The level of maturity was unknown in the other 25 cases. The characteristics of the 27 patients are listed in Table 3. The mean age was relatively young (50 years), and slight male predominance was seen, with a male : female ratio of 8 : 5. As many as 12 patients had IgG-type M-protein, followed by IgA-type (n = 6) and Bence-Jones protein-type (n = 2). Eleven patients had κ-type, and 3 had λ-type. According to the Durie & Salmon staging system, 1 patient was classified into stage II and 8 patients were classified into stage III. An advanced stage of IgG κ-type extramedullary plasmacytoma was often seen in relatively young men. These patients received a variety of pretreatments, and thalidomide was considered to be effective regardless of the pretreatment. The interval from diagnosis to the initiation of thalidomide treatment was approximately 33 months, suggesting that thalidomide is effective even after the early stages of the disease. However, in the present case, thalidomide was started at an early stage of the disease (approximately 3 months). The mean daily dose of thalidomide was approximately 363 mg, suggesting that a relatively high dose is required. Many patients (11 out of 27) received dexamethasone as a concomitant drug. The mean interval from the initiation of thalidomide to the appearance of an effect was 2.0 months, and the mean duration of the effect was relatively short (6.2 months). Thus, the effect of thalidomide was obtained within a short time. In the present case, the effect of thalidomide was quickly observed (after approximately 0.5 months), but the duration of the effect was relatively short (approximately 7 months), consistent with previous reports. As for the outcomes, 12 patients survived and 5 died. After the disappearance of the effect of thalidomide, the subsequent treatments were effective in some cases. Subsequent treatment strategies need to be further developed, as thalidomide is only effective for a short period and the patient prognosis is poor.

Plasmablastic plasmacytoma was analyzed in 15 cases, and this disease is known to have a poor prognosis with a mean survival time of approximately 10 months.[2] In addition, immature myeloma may be resistant to thalidomide.[3]

In the present case, thalidomide was effective against extramedullary plasmablastic plasmacytoma for a short period of time, but this was considered to be rare. CD45 and MPC-1 are known to be negative in immature plasma cells.[1] The present case, which was successfully treated with thalidomide, had somewhat immature ($CD45^+$, $MPC\text{-}1^-$, and

Table 2. Cases reporting efficacy of thalidomide (Thal) for extramedullary masses

Case	Age/Sex	Disease type	Stage (DS)	Pretreatment	Interval from diagnosis to initiation of Thal (months)	Dose (mg)	Concomitant drug	Interval from initiation of Thal to the appearance of the effect (months)	Duration of effect (months)	Outcome	Year of report	Ref.
1	56/male	IgGκ	IIIA	DEX/CHOP/VCAP	3	100	DEX	0.5	7	death	2011	present report
2	73/female	IgGκ	IIIA	MP/Rx	24	100	none	2	10, ongoing	survival	2010	14
3	70/female	IgAλ	IIIA	MP/Rx/VAD/MCNU-VMP	31	100	PSL	0.25	3	death	2010	14
4	55/male	?κ	IIA	VAD/WBI	5	200	DEX	NA	6	death	2010	15
5	40/male	IgGκ	?	WBI	2	200	DEX	NA	2, ongoing	survival	2010	15
6	74/male	IgGκ	IIIA	MP/DEX/VAD	32	100→200→100→200	DEX	1	3	death	2009	9
7	58/male	IgGκ	NA	VAD/EDAP/Rx	32	100→400	Bor/DEX	3.1	9	survival	2008	16
8	58/female	IgGκ	IIIA	Rx/VAD	11	200	DEX/ASCT	2	14	survival	2007	17
9	78/female	IgGκ	NA	MP	72	200→100	DEX	2	6	survival	2006	18
10	60/male	IgGκ	IIIA	VAD/Rx/MP	13	200	DEX/Rx	few	9	survival	2004	19
11	65/?	NA	NA	Chemo/Rx	NA	200- 800	DEX/CPA	NA	n = 1 ; 6	NA	2002	20
12	58/?	PJP?	NA	NA	96	200- 800	DEX/CPA	NA	n = 1 ; 2	NA	2002	20
13	60/?	IgAλ	NA	ASCT/Rx/VNR	NA	200- 800	DEX/CPA	NA	n = 1 ; 5	NA	2002	20
14	42/male	PJPκ	III	Rx/MP/alloBMT	48	800	IFN	NA	11	survival	2001	21
15	49/male	IgAλ	NA	Chemo/alloBMT/DLI/Rx/DEX	60	400	none	3	7	survival	2001	21
16	45/female	?κ	III	Chemo/alloBMT/Rx/DEX	36	300	none	4	4	survival	2001	21
17-24	NA : n = 8	n = 4 ; IgG n = 3 ; IgA n = 1 ; light-chain	NA : n = 11	NA : n = 11	NA : n = 11	NA : n = 11	NA : n = 11	NA : n = 11	n = 5 ; 4, n = 2 ; 7, n = 1 ; 10	NA : n = 11	2005	22
25-27	NA : n = 3	NA : n = 3	NA : n = 3	NA : n = 3	NA : n = 3	NA : n = 3	n = 1 ; Orchidectomy + DEX n = 2 ; Rx	NA : n = 3	NA : n = 3	n = 2 ; survival, n = 1 ; death	2005	23

DEX, dexamethasone ; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisolone ; VCAP, vincristine, cyclophosphamide, doxorubicin, and prednisolone ; MP, melphalan and prednisolone ; Bor, bortezomib ; Rx, radiation ; CPA, cyclophosphamide ; VAD, vincristine and doxorubicin ; ASCT, auto stem cell transplantation ; DEX, dexamethasone ; MCNU-VMP, ranimustine, vindesine, melphalan, and prednisolone ; PSL, prednisolone ; WBI, whole body irradiation ; NA, not available ; EDAP, etoposide, cytarabine, dexamethasone, and cisplatin ; chemo, chmotherapy ; VNR, vinorelbine ; alloBMT, allo bone marrow transplant ; IFN, interferon ; DLI, donor lymphocyte infusion ; Mel, melphalan

Table 3. Characteristics of 28 patients whose extramedullary masses were effectively treated with thalidomide

Age	50.9 (40 78)	n = 16, unknown : 11
Male : female ratio	8 : 5	n = 13, unknown : 13
Disease type (heavy chain)	IgG : 12, IgA : 6, IgD : 0, IgE : 0, BJP : 2	n = 20, unknown : 7
Disease type (κ/λ)	κ : 11, λ : 3	n = 14, unknown : 13
Stage (DS)	I : 0, II : 1, III : 8	n = 9, unknown : 18
Pretreatment	Rx : 12, DEX : 3, chemo : 20, Auto : 1, allo BMT : 3, Bor : 1, DLI : 1	n = 40, unknown : 12
Interval from diagnosis to initiation of Thal (months)	33.2 (2 96)	n = 14, unknown : 13
Dose (mg)	362.5 (100-800)	n = 16, unknown : 12
Concomitant drug	Rx : 2, DEX : 12, PSL : 1, chemo : 4, Bor : 1, ASCT : 1, IFN : 1, orchidectomy : 1, none : 3	n = 24, unknown : 8
Interval from initiation of Thal to the appearance of the effect (months)	2.0 (0.25 4)	n = 9, unknown : 18
Duration of effect (months)	6.2 (2614) including ongoing cases	n = 24, unknown : 4
Outcome	survival : 11, death : 5	n = 16, unknown : 11

Thal, thalidomide ; Rx, radiation ; DEX, dexamethasone ; chemo, chmotherapy ; ASCT, auto stem cell transplantation ; allo BMT, allo bone marrow transplant ; Bor, bortezomib ; DLI, donor lymphocyte infusion ; PSL, prednisolone ; IFN, interferon

CD49e$^-$) extramedullary plasmablastic plasmacytomas (Fig. 3d & 3e) at first. However, at the time of recurrence after the patient had become resistant to thalidomide, a biopsy and autopsy examination of the extramedullary mass in the left neck revealed MPC-1 partial positivity and CD45 negativity, indicating that the extramedullary plasmablastic plasmacytoma had reverted to a more immature state (Fig. 3i). CD49e negativity continued to be observed (Fig. 3j). CD45$^+$ plasma cells are known to be more immature than CD45$^+$ ones and do not easily undergo apoptosis.[1] In the present case, the nega-

tive conversion of CD45 may have caused resistance to apoptosis and to thalidomide. $CD45^-$ immature plasma cells reportedly differentiate into $CD45^+$ mature plasma cells in the presence of interleukin (IL)-6.[1] Considering this report, we speculated that the CD45 negativity occurred because thalidomide inhibited IL-6. However, while one report has described that thalidomide inhibits IL-6,[12] another has described that thalidomide does not affect IL-6.[13] Since we did not measure IL-6 in this case, we were not able to draw any conclusions on this issue. Therefore, further analysis is required in the future. Thalidomide may be effective against immature extramedullary plasmablastic plasmacytoma if CD45 is positive.

In the future, a study of additional thalidomide-treated cases, in which the presence of cell surface CD45 and MPC-1 has been examined to determine the maturity of plasma cells, is needed. In addition, the mechanism responsible for the reduction in thalidomide efficacy should be investigated by sequentially assessing the cell maturity and expression of IL-6 through the examination of cell surface markers at the time of the decrease in efficacy.

CONSENT

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

COMPETING INTERESTS

The authors declare that they have no competing interests.

AUTHORS' CONTRIBUTIONS

YS treated the patient, collected and analyzed data, and wrote the manuscript. TA, AS, HI, MW, and KS treated the patient and collected the data. NN and TS analyzed the data. NK and MN provided guidance to YS for preparation of this manuscript. All authors read and approved the final manuscript.

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