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【 CASE REPORT 】

Multiple Myeloma with Central Nervous System Relapse Early after Autologous Stem Cell Transplantation: A Case Report and Literature Review

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Abstract:
Few reports have so far described central nervous system (CNS) involvement in multiple myeloma (MM), which shows a poor prognosis owing to its resistance to several treatments. We herein describe a 45-year-old woman who had MM (diagnosed with IgA-κ type) with CNS relapse early after undergoing autologous hematopoietic stem cell transplantation. Because no standard treatment for CNS lesions of MM has been established, we conducted a literature review on the cerebrospinal fluid (CSF) transferability of drugs for MM, since it was considered to be a useful tool for CNS involvement. Immunomodulatory-drugs including pomalidomide exhibit a good CSF transfer ability, and, therefore, may be beneficial against the CNS involvement of MM.

Key words: multiple myeloma, central nerves system, pomalidmide, intrathecal chemotherapy, craniospinal radiation

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Introduction

Previous studies have shown that the multiple myeloma (MM) genome is complex, and that MM patients have extremely diverse cytogenetic abnormalities with genomic heterogeneity (1). Thus, MM demonstrates a highly variable clinical course. Few reports have so far described neurologic complications arising from direct MM cell involvement in the central nervous system (CNS) (2-6). We herein present a case of an MM patient with an early relapse localized in the CNS early after autologous hematopoietic stem cell transplantation (ASCT). Because no standard treatment for CNS lesions of MM has yet been established (5, 7) due to a lack of evidence, we conducted a literature review on the cerebrospinal fluid (CSF) transferablity of drugs for MM. The current case demonstrates that such a presentation of MM can be successfully treated with pomalidomide-dexamethasone (Pd) therapy together with whole-brain and craniospinal irradiation and intrathecal chemotherapy.

Case Report

A 45-year-old woman with M-proteinemia, anemia, and hypercalcemia was referred to our hospital. The patient had initially noticed general pain and consulted her physician. Other than her performance status being affected by general pain, the general and neurologic examination was unremarkable. A blood examination showed anemia, hypercalcemia, and elevated lactate dehydrogenase (LDH), and IgA-κ type M protein was detected by serum protein immunoelectrophoresis (Table 1). Bone marrow (BM) specimens revealed 25.7% of atypical plasma cells with the expression of CD38, CD56, and CD138, but no expression of CD19, CD20, MPC-1, CD45, or CD49e, which was compatible with a diagnosis of MM. Chromosome and fluorescence in situ hybridization cytogenic examinations of the BM showed complicated karyotypes, 72% IgH/FGFR3 fusion and 72% deletion 13q signal-positive cells, but no deletion of either 17p or IgH/MAF fusion. Diffusion-weighted whole-body imag-

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Table 1. Hematologic Assessment of Patient.

WBC	6,400 /μL	BUN	19 mg/dL	LDH	561 U/L	<Urine>	
Neutro	67.0 %	Cre	0.62 mg/dL	CK	23 U/L	gravity	1.010
Baso	0.0 %	Na	142 mEq/L	CRP	4.753 mg/dL	WBC	(-)
Eosino	0.5 %	K	4.1 mEq/L			urobilinogen	normal
Lympho	14.0 %	Cl	97 mEq/L	APTT	33.7 s	Uric protein	(-)
Mono	9.5 %	UA	5.1 mg/dL	PT-INR	1.16	pH	5.5
Blast	1.0 %	Ca	11.3 mg/dL	IgG	245 mg/dL	Uric blood	(+/-)
Pro-myelo	0.0 %	Tp	8.4 mg/dL	IgA	2,381 mg/dL	ketone	(+/-)
Myelo	6.5 %	ALB	3.6 g/dL	IgM	31 mg/dL	bilirubin	(+/-)
Meta-myelo	1.5 %	AST	31 U/L	β2-MG	7.1 mg/L	glucose	(+/-)
RBC	295×10^4 /μL	ALT	9 U/L	IEP	IgA-κ	Bence Jones protein	(+)
Hb	8.5 g/dL	ChE	237 U/L	FLC κ/λ	31.06		
Hct	27.1 %	T-Bil	0.6 mg/dL	κ chain	61.5 mg/mL		
Reticulo	0.4 %	ALP	215 U/L	λ chain	1.98 mg/mL		
PLT	16.2×10^4 /μL	γGTP	20 U/L				

IEP: immunoelectrophoresis, FLC: free light chain, PT-INR: prothrombin time-international normalized ratio

ing with background body signal suppression (DWIBS) detected diffuse abnormal signals in BM including in many vertebrae. From these findings, MM was diagnosed according to the Revised-International Staging System III (8).

Treatment with bortezomib-dexamethasone (Bd) therapy (1.3 mg/m^2 bortezomib twice a week and 40 mg dexamethasone per week) was started, but it proved to be ineffective. The addition of lenalidomide administration [25 mg/day (on days 1-21)] with Bd transiently decreased the IgA levels. However, 1 week after the addition of lenalidomide, the right femoral diaphysis became fractured, and surgery was thus performed. After surgery, carfilzomib-lenalidomide-dexamethasone (CLd) therapy [with at a dose and schedule according to the ASPIRE protocol (9)] was started. After three courses of CLd therapy, a stringent complete response (sCR) was achieved. High-dose melphalan (200 mg/m^2) therapy with ASCT was performed at 9 months after the initial diagnosis, and then the patient maintained an sCR after ASCT, which was confirmed by a BM biopsy and DWIBS. Lenalidomide maintenance therapy (10 mg orally) was then started. Approximately 2 months after ASCT, severe headache, nausea, and vomiting suddenly appeared, and the patient was hospitalized. A CSF examination revealed a marked increase in the total cell count (441/μL), completely consisting of abnormal plasma cells (Fig. 1A), and increased total protein (61 mg/dL) and decreased sugar levels (26 mg/dL). An examination of the plasma cell clonality of the CSF showed expression of CD38, CD56, and CD138 but not CD19, CD20, MPC-1, CD45 or CD49e (Fig. 1B), which was the same result found for the MM cells in BM at diagnosis. Bacterial culture, a tuberculosis PCR test, and viral gene PCR tests including herpes virus were all negative. Although no lesions could be detected by head computed tomography, magnetic resonance imaging (MRI) revealed patchy hyperintense regions on T2-weighted images (Fig. 2). These findings were indicative of MM involvement in the CNS. Blood examinations showed no anemia, renal dysfunction, or hypercalcemia. M-protein was not detected by serum protein immunoelectrophoresis. No abnormal increase in the plasma cells was observed, and no cells with IgH/FGFR3 fusion or a deletion of 13q signals were detected in BM specimens. No systemic lesions were detected on DWIBS. These findings indicate that the relapse was localized to the CNS.

Dexamethasone monotherapy was started, and the intrathecal injection of methotrexate (15 mg), cytarabine (40 mg), and dexamethasone (4 mg) was performed twice a week, four times in total. Thereafter, Pd therapy with 3 mg pomalidomide and 40 mg dexamethasone [performed on a schedule according to the MM-003 protocol (10)] with whole-brain/craniospinal irradiation (27 Gy/15 fr) was started. The number of myeloma cells in the CSF rapidly decreased, and the cells were observed to have disappeared at the end of irradiation. However, Pd therapy was transiently discontinued 10 days later because of myelosuppression and then was again resumed and continued after the completion of whole-brain/spinal irradiation. Thereafter, no further relapse was observed (Fig. 3).

Three months later, DWIBS revealed a mass lesion around the right kidney, which was indicative of extramedullary recurrence, but no relapse of the CNS lesions. Three courses of daratumumab-lenalidomide-dexamethasone therapy [with a dose and schedule according to the POLLUX protocol (11)] were performed, but no reductive effect on the abdominal tumor was observed. Thereafter, conventional chemotherapy [PACE (cisplatin, 10 mg/m^2/day; doxorubicin, 10 mg/m^2/day; cyclophosphamide, 400 mg/m^2/day; and etoposide, 40 mg/m^2/day from days 1 to 4)] was temporarily effective, but the tumor recurred, and the patient eventually died 12 months after the onset of CNS relapse (21 months after the diagnosis of MM). After the onset of the abdominal lesion, no relapse of the CNS lesions was observed.

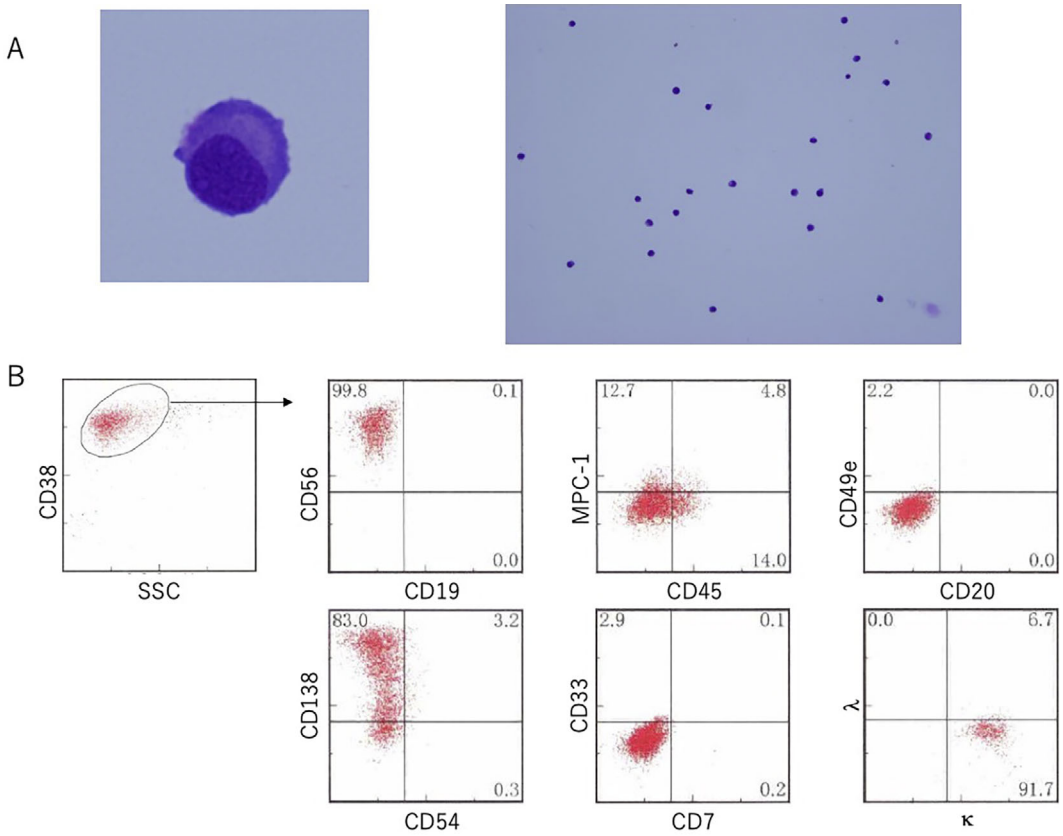

Figure 1. **Cerebrospinal fluid specimens showing a marked increase in the total cell count (441/μL), completely consisting of abnormal plasma cells. A: May-Giemsa staining ×400 and ×20 original magnification. B: A flow cytometric analysis of CD38-positive CSF cells. CSF: cerebrospinal fluid, SSC: side scatter**

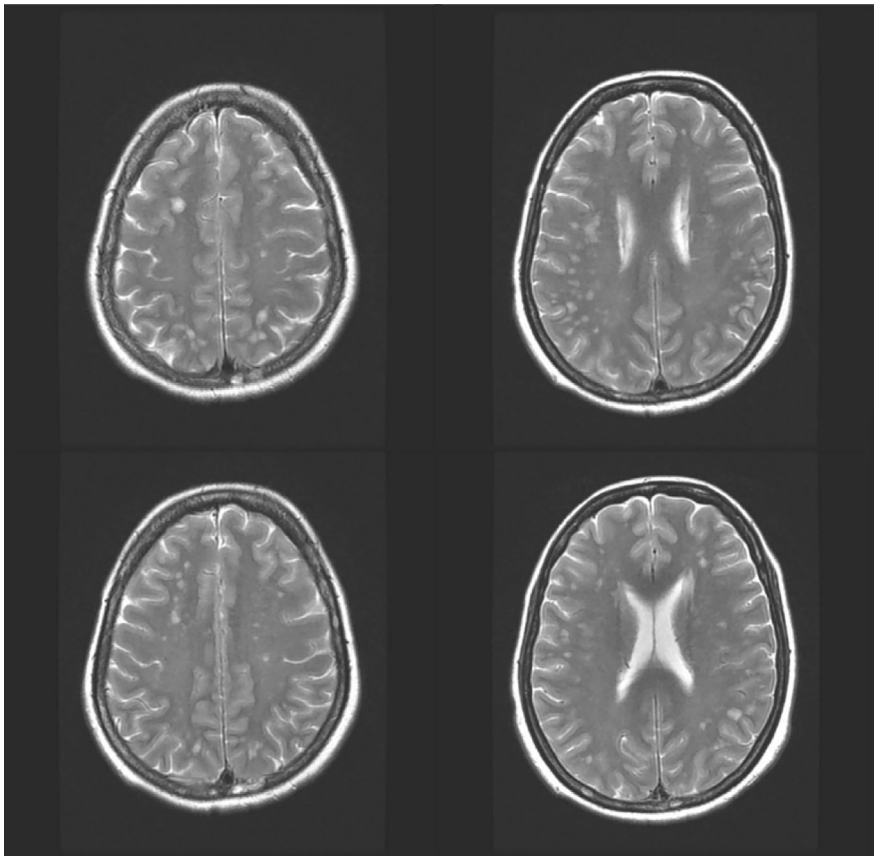

Figure 2. **Magnetic resonance imaging showing patchy hyperintense on T2-weighted images.**

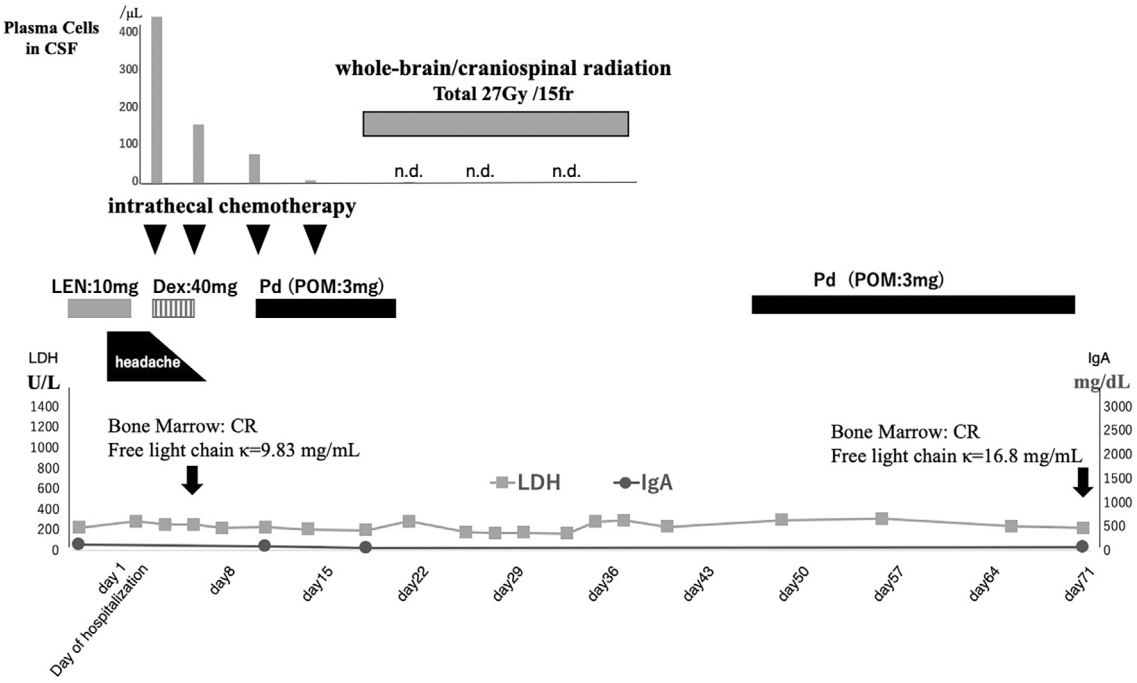

Figure 3. **Clinical course from the onset of central nervous system relapse. End of July (day1; day of hospitalization) (approximately 2 months after autologous stem cell transplantation), the patient experienced severe headache, nausea, and vomiting, and then dexamethasone monotherapy and intrathecal injection of methotrexate, cytarabine, and dexamethasone were started. Pomalidomide-dexamethasone (Pd) therapy and whole-brain/craniospinal irradiation were started on Day9 and Day17, respectively. Pd therapy was transiently discontinued because of myelosuppression and resumed on Day46. CSF: cerebrospinal fluid, LEN: lenalidomide, POM: pomalidomide, DEX dexamethasone, Pd: pomalidomide-dexamethasone, n.d.: not detected**

Discussion

In MM, extramedullary lesions emerge in approximately 6-8% of cases at the time of diagnosis and in approximately 10-30% of cases in the advanced or relapse stage (12, 13), but the frequency of CNS involvement is only approximately 1% (2-6). The clinical symptoms of CNS involvement in MM are diverse and uncharacteristic, including headache, nausea, vomiting, consciousness disorder, limb weakness, and convulsions (14). Because these symptoms are similar to those of hypercalcemia, uremia, and hyperviscosity syndrome or side effects caused by chemotherapy, a CSF examination to confirm the presence of MM cells in addition to MRI is crucial for making an accurate diagnosis (14). Moreover, the detection of abnormal free light chain in the CSF has great diagnostic significance (15), even if myeloma cells are absent in CSF. MRI may show high-intensity portions of the meninges and formation of solid tumors in the brain.

Although it is difficult to predict the CNS involvement of MM, features of CNS involvement include high-risk chromosomal abnormalities, high LDH levels, high β2 microglobulin levels, extramedullary lesions, and leukemic change (4, 5). In particular, a high frequency of chromosomal deletion 17p or deletion 13q has been reported (16, 17). The median age at the time of the initial diagnosis of MM patients, who develop CNS involvement during the clinical course, is 54-64 years (2-6), which is relatively younger than the age of onset of MM, as was seen in our case. The early onset of MM may be an important indicator of CNS involvement. Abdallah et al. reported that 42.9% of patients develop CNS involvement during the progression stage of relapsed MM, 48.6% of patients in the stable stage during treatment, and 8.6% of patients in the remission state (14). The average latency period from MM diagnosis to diagnosis of CNS involvement is 15 months, and the latency is 32.1 months in patients with ASCT, which is longer than that in patients without ASCT (8.3 months) (14). Our patient had a younger age, an aggressive disease course with resistance to bortezomib, and high-risk chromosomal abnormalities, thus suggesting a poor prognosis. Indeed, the latent period of between MM diagnosis and onset of CNS relapse was 11 months, which is very short. Furthermore, two months after ASCT, the tumor recurred only in the CNS despite hematologic remission. Thus, if unexplained neurological findings occur at any time during the disease course in patients with risk factors for CNS involvement, then either MRI or a CSF examination should be promptly performed for verification.

Although newly developed therapeutic agents have improved the prognosis of MM, no standard treatment for CNS involvement has yet been established, and the prognosis is

Table 2. Data of CSF Transferability and Efficacy of MM Drugs.

Drugs		CSF transferability	Cases for CNS involvement of MM
IMiDs	Thalidomide	good[18, 23]	effective[18, 21, 22, 28]
	Lenalidomide	good[19, 23]	effective[19, 20, 28]
	Pomalidomide	good[24]	effective[25, 26]
Proteasome inhibitors	Bortezomib	poor[30]	ineffective[30]
	Carfilzomib	poor*	no data
	Ixazomib	poor*	no data
Antibody-drugs	Daratumumab	good[32]	effective[32, 33, 34]
	Isatuximab	no data	no data
	Elotuzumab	no data	no data

*no experimental data exist.

very poor, with a median overall survival (OS) of less than 3-6 months (2-6). According to our literature review on CSF transfer of drugs for MM, immunomodulatory drugs (IMiDs) have CSF transferability (Table 2). Cases of successful treatment with thalidomide or lenalidomide have been reported (3, 18-20). Thalidomide can be detected in CSF after an oral administration (18, 21, 22), and lenalidomide can cross the blood-brain barrier (BBB) (19, 20, 23). In particular, reports have shown that pomalidomide has good CSF transferability (24-26) and activity in extramedullary disease (27). In addition, Chen et al. reported that six of nine long-term survivors (median OS of 17.1 months) with CNS involvement received IMiDs-based therapy combined with intrathecal chemotherapy plus irradiation and/or systemic chemotherapy (28). Intrathecal chemotherapy is often effective against various hematological malignancies and CNS involvement of MM (15). Although a rapid therapeutic effect can be obtained, a long-term therapeutic effect of intrathecal chemotherapy is difficult to maintain. Thus, this therapy should be used as a bridge for subsequent systemic therapy. Moreover, MM cells are highly radiosensitive (29); thus, radiotherapy is also effective for CNS involvement and it is also more effective when combined with chemotherapy (3). In the present case, because of recurrence after CLd and lenalidomide maintenance therapy, pomalidomide was used instead of lenalidomide treatment. Because there was no recurrence in the CNS, combination therapy with pomalidomide, radiotherapy, and intrathecal chemotherapy was considered to be effective in our patient.

One case report showed the inefficacy of bortezomib therapy for CNS involvement of MM because of its poor CSF transferability (30). In general, proteasome inhibitors such as carfilzomib and ixazomib have a good ability to permeate throughout the body tissues but cannot penetrate BBB (Table 2); thus, there are no data on the efficacy of carfilzomib and ixazomib for CNS lesions. However, the use of bortezomib has been reported to enhance radiosensitivity and chemosensitivity (31), and studies of CNS lesion treatment with combination therapy including bortezomib should be conducted in the future. To our knowledge, one report examined the CSF transferability of daratumumab (32), and two case reports described significant activity of daratumumab for CNS lesions of MM when concomitantly used with intrathecal chemotherapy (33, 34). There are no current data of CSF transferability and the effectiveness of isatuximab and elotuzumab for CNS lesions.

It is possible that the induction of CLd followed by high-dose melphalan chemotherapy of ASCT might have insufficient CNS effects, because proteasome inhibitors carfilzomib has less CNS transferability and alkylating agents such as cyclophosphamide or melphalan can poorly penetrate the CSF (6). We speculated that the initial clones of MM in our case may have escaped into and grown locally in the CNS, where the drugs had not sufficiently penetrated, thus resulting in a local early relapse.

Conclusion

CNS involvement, as seen in our case, is an important consideration for patients with a younger disease onset and risk factors such as chromosomal abnormalities which predict a poor prognosis and high LDH levels. Regardless of hematological remission, when CNS symptoms develop, it is necessary to actively search for CNS lesions by a CSF examination and head MRI. MM patients with CNS lesions have a poor prognosis, but IMiDs such as pomalidomide may be effective because of their CSF transferability; thus, it may be beneficial to administer combination therapies including IMiDs, radiotherapy, and intrathecal chemotherapy against MM with CNS involvement. Crucial data are still sparse regarding treatment, and the accumulation of data from more cases is important to verify the choice of combination drugs for CNS lesions of MM.

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