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Case Report

Withdrawal from Hemodialysis in a Patient with IgD Type Multiple Myeloma: A Case-based Review

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Several previous case reports have shown that patients with immunoglobulin D (IgD) multiple myeloma (MM) can be withdrawn from hemodialysis, however, the characteristics that can predict withdrawal in these patients have not yet been elucidated. A 57-year-old Japanese woman required hemodialysis because of renal dysfunction due to IgD-λ and Bence Jones protein-λ MM. Bortezomib-based chemotherapy nine days after admission led to her withdrawal from hemodialysis on Day 50. In our case-based review, younger age and early initiation of bortezomib-based chemotherapy emerged as possible predictors of successful hemodialysis withdrawal.

Key words: IgD-type multiple myeloma, acute renal dysfunction, urinary protein, hemodialysis, bortezomib

Multiple myeloma (MM) is a hematopoietic tumor characterized by the monoclonal growth of plasma cells in the bone marrow. Approximately 20-40% of patients with MM develop renal dysfunction and 10% require hemodialysis due to the monoclonal immunoglobulin (M-protein) produced by tumor cells [1].

Immunoglobulin D (IgD)-MM is a rare subtype that accounts for approximately 2% of MM cases [2]. Previous reports have revealed that patients with IgD-MM have Bence Jones protein (BJP), hypercalcemia, and severe renal dysfunction more frequently than those with other MM types [3-5]. Although a few case reports have shown that patients with IgD-MM can be withdrawn from hemodialysis [6,7], the characteristics that can predict this withdrawal have not yet been elucidated.

In this case-based review, we report the case of a patient with IgD-MM, who presented with acute renal failure and required hemodialysis. The patient was successfully withdrawn from hemodialysis using bortezomib-based chemotherapy. We review previous reports and discuss predictive factors for the withdrawal from hemodialysis of patients with IgD-MM.

Case Presentation

A 57-year-old Japanese woman visited a local doctor with anorexia, nausea, and weight loss. The patient was referred to our hospital and admitted because of high serum creatinine (s-Cr) levels. She had no relevant medical history. The physical examination findings were as follows: height, 167 cm; body weight, 64.8 kg (–5 kg for three months); body temperature, 36.8°C; blood pressure, 175/116 mmHg; pulse, 92 beats/min

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and regular; and respiration rate, 20 /min. The patient was conscious and responsive. Her eyelid conjunctiva indicated anemia. A systolic murmur was audible at the strongest point of the left margin of the sternum in the fourth intercostal space. The patient's abdomen was flat and soft. There were no rashes, edema, or arthritis of the extremities. Urinary volume upon admission was 1,500 mL/day without diuretics.

Laboratory tests yielded the following results: hemoglobin, 7.6 g/dL; total protein, 8.7 g/dL; albumin, 4.3 g/dL; lactate dehydrogenase, 155 U/L; urea nitrogen, 55.5 mg/dL; s-Cr, 8.50 mg/dL; estimated glomerular filtration rate, 4.44 mL/min; β2-microglobulin, 48.1 mg/L; serum calcium, 9.9 mg/dL; serum IgG, 1,352 mg/dL; IgA, 59 mg/dL; IgM, 33 mg/dL; C-reactive protein, 3.51 mg/dL; and serum ferritin, 1,857 ng/mL. There was a discrepancy in urinary protein levels as assessed by quantitative (6.68 g/gCr) and semi-quantitative (1+) urinalysis, indicating the presence of urinary proteins other than albumin. The urinary protein fraction showed a sharp peak in the β-γ fraction. The fractional excretion of sodium was 5.76% (>2%), suggesting intrinsic renal injury. Computed tomography revealed no bilateral renal atrophy, pyelectasia, neoplastic lesions, or bone lesions. IgD-λ and BJP-λ were detected by urinary and serum M-protein immunofixation electrophoresis. Serum-free κ light chain levels were 93.3 mg/L while serum-free λ light chain (sFLC-λ) levels were increased at 13,860 mg/L (serum-free κ: λ ratio: <0.01).

Bone marrow aspiration performed on Day 6 demonstrated the proliferation of large plasma cells with distinct nucleoli, which accounted for 30.6% of all nuclear cells (Fig. 1). The patient was finally diagnosed with IgD-λ+BJP-λ-type MM. Because of the complex karyotype and amplification of chromosome band 1q21, she was classified according to the International Staging System for Multiple Myeloma (ISS) as Stage III, and as Stage II under the Revised-ISS [8].

Hemodialysis was initiated on Day 7 because of uremia, and chemotherapy with bortezomib and dexamethasone (BD) was administered on Day 9 (Fig. 2). On Day 32, the patient showed partial response to the treatment, which is defined as a >50% reduction in serum M-protein and a >90% reduction in urinary M-protein in 24 h or to <200 mg in 24 h [9]. The patient's s-Cr and sFLC-λ levels decreased to 5.37 mg/dL and 1,460 mg/L, respectively. On Day 33, chemotherapy with daratumumab in addition to BD was initiated to intensify the treatment.

On Day 50, the patient's s-Cr level decreased to 2.71 mg/dL and she could finally be withdrawn from hemodialysis. With continuation of the same treatment, the patient achieved a very good partial response, which is characterized by the detection of serum and urinary M-protein by immunofixation but not by electrophoresis, or a >90% reduction in serum M-protein in addition to a urinary M-protein level of <100 mg in 24 h [9].

Discussion

We encountered a patient with IgD-MM, who presented with acute renal failure and required hemodialysis. The patient was successfully withdrawn from hemodialysis with bortezomib-based chemotherapy.

The early initiation of treatment in younger patients with IgD-MM may contribute to a successful withdrawal from hemodialysis. Previous reports of patients with all types of MM have found that factors such as sFLC and serum β2-microglobulin levels, time from the detection of renal dysfunction to initial treatment of MM, treatment response, and age are associated with withdrawal from hemodialysis [10, 11]. Severe renal dysfunction develops more frequently in patients with IgD-MM than in those with other types of MM, but, to the best of our knowledge, no difference in renal recovery between IgD-MM and the other types of MM has yet been reported [3, 4] and, despite the frequent devel-

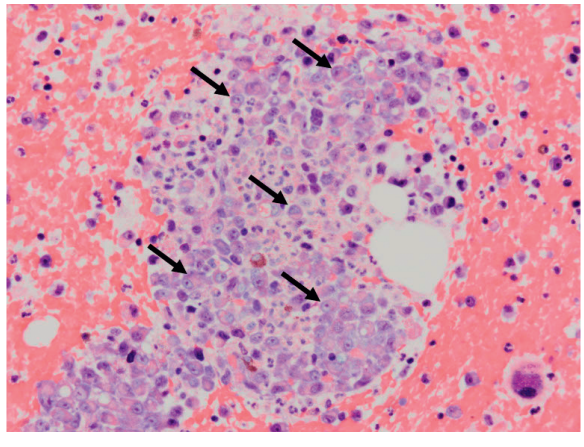

Fig. 1 Bone marrow aspiration findings. May-Giemsa staining showing the proliferation of large plasma cells with distinct nucleoli (arrow) in the bone marrow.

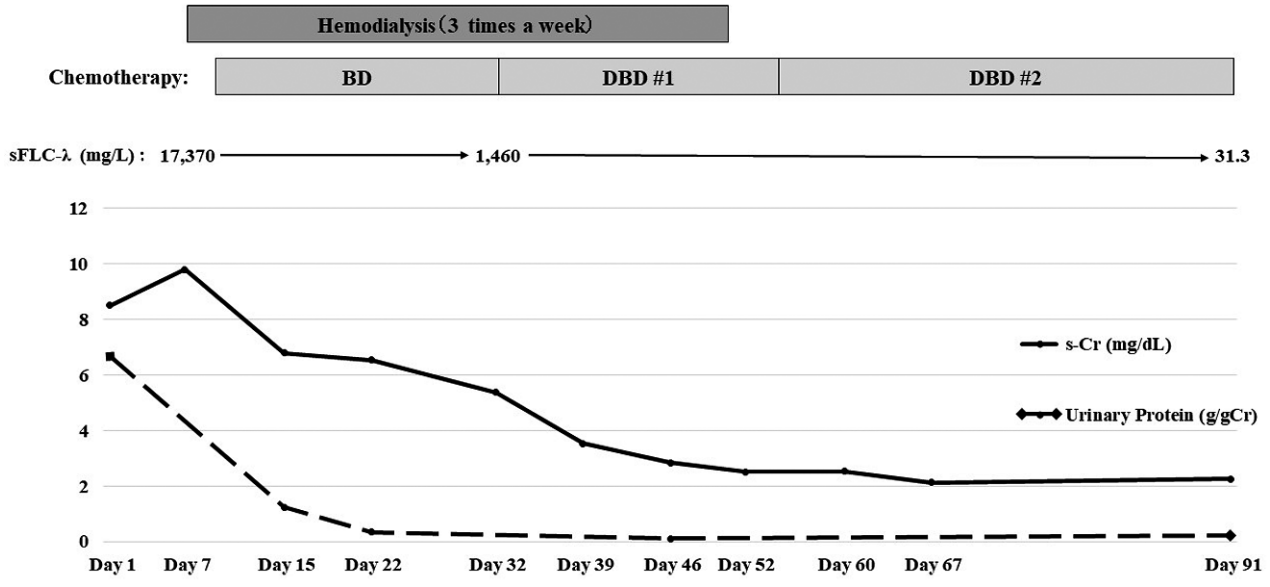

Fig. 2 Clinical course. BD, bortezomib and dexamethasone; DBD, daratumumab, bortezomib and dexamethasone; sFLC-λ, serum-free λ light chain; s-Cr, serum creatinine.

opment of severe renal dysfunction in patients with IgD-MM, no previous reports have explored its predictors in these patients. To analyze candidate predictors for withdrawal from hemodialysis, we used the PubMed/Medline database to identify 11 cases in nine reports of newly diagnosed IgD-MM patients requiring hemodialysis using the following search strategy:

#1 Add Search "Multiple myeloma" [mh]
#2 Add Search "dialysis" [mh]
#3 Add Search "renal insufficiency" [mh]
#4 Add Search "renal dialysis" [mh]
#5 Add Search #2 OR #3 OR #4
#6 Add Search IgD
#7 Add Search #1 AND #5 AND #6.

A summary of these previous reports and the present case is shown in Table 1 [6,7,12-17]. Of the 12 patients, including the present case, only three (25%), all of younger age (<65 years), were successfully withdrawn from hemodialysis. Because IgD is not evaluated in common clinical practice, early diagnosis is difficult, which delays the initiation of treatment. In our case, the discrepancy in urinary protein levels as assessed by quantitative and semi-quantitative urinalysis contributed to an early diagnosis; hence, the treatment for IgD-MM was initiated on Day 9 after admission. In a previous report, the mean time from the detection of renal dysfunction to treatment initiation in patients who required hemodialysis was 1 month (range: 0.25-7 months) [10]. Therefore, early diagnosis and treatment initiation could have contributed to the success of our patient's withdrawal from hemodialysis. As in the present case, detecting non-albumin proteinuria in patients with renal impairment may help with the early diagnosis and treatment of IgD-MM.

Furthermore, bortezomib-based chemotherapy is suggested as a first-line treatment for IgD-MM patients requiring hemodialysis. Although it remains unknown whether bortezomib treatment is more effective in patients with IgD-MM than in those with other types of MM, the International Myeloma Working Group guideline recommends bortezomib as a first-line treatment for MM patients with renal dysfunction [18], and several studies have reported the benefit of bortezomib-based chemotherapy for MM patients with renal failure [10,11,19-21]. Cast nephropathy by sFLC, direct damage of the tubules by sFLC, and amyloidosis are the main causes of renal dysfunction in patients with MM [1,22]. Previous reports have found that most patients with amyloidosis had nephrotic syndrome [23], while patients with cast nephropathy often showed acute kidney injury with proteinuria mainly consisting of light chains without nephrotic syndrome [1]. To the best of our knowledge, the frequency of causes of renal failure among the various types of MM

Table 1 The summary of this case and previous 11 cases of newly diagnosed IgD type multiple myeloma requiring hemodialysis

	Age	Sex	Cr [mg/dL]	sFLC κ/λ [mg/dL]	Plasma cell ratio [%]	Bone lesions	ISS stage	Withdrawal date of dialysis	Outcome	First chemotherapy regimen	Initiation date of chemotherapy
This Case	52	Female	8.5	93.3/13,860	30.6	Negative	Ⅲ	Day 50	Alive	Bd	Day 9
Case 1[16]	53	Female	23.3	19/2,500	70	Positive	Ⅲ	Day 34	Alive	Bd	Day 20
Case 2[7]	45	Female	18.32	146/13	80	Positive	N/A	Day 154	Alive	VCD	N/A
Case 3[12]	62	Male	5.99	N/A/8,948	70–80	Positive	N/A	N/W	Alive	Bd	N/A
Case 4[13]	78	Male	3.76	N/A/4,250	50	N/A	N/A	N/W	Alive	VRd	N/A
Case 5[14]	28	Female	10.6	N/A	N/A (dry tap)	N/A	N/A	N/W	Death	Cy+PSL	N/A
Case 6[14]	52	Male	10.6	N/A	N/A	Positive	N/A	N/W	Death	None	Not applicable
Case 7[15]	74	Male	7.6	N/A	>50	N/A	Ⅲ	N/W	Death	VAD	N/A
Case 8[15]	74	Female	9.5	N/A/3,045	>50	N/A	Ⅲ	N/W	Death	DT	N/A
Case 9[15]	74	Male	8	N/A/13,900	>50	N/A	Ⅲ	N/W	Alive	VAD	N/A
Case 10[16]	64	Male	6.4	N/A	94.4	Negative	Unknown	N/W	Death	VMP	N/A
Case 11[17]	37	Male	15.9	N/A (ratio 1 : 13)	100	N/A	Unknown	N/W	Alive	PAD	N/A

sFLC, Serum-free light chain; ISS, International Staging System; ASCT, Autologous stem cell transplantation; Bd, Bortezomib+Dexamethasone; VCD, Bortezomib+Cyclophosphamide+Dexamethasone; VRd, Bortezomib+Lenalidomide+Dexamethasone; Cy, Cyclophosphamide; PSL, Prednisolone; VAD, Vincristine+Doxorubicin+Dexamethasone; DT, Dexamethasone+Thalidomide; VMP, Bortezomib+Melphalan+Prednisolone; PAD, Bortezomib+Doxorubicin+Dexamethasone; N/A, Not Available; N/W, Not Withdrawal.

has not yet been reported. Since the present case had massive urinary protein with a sharp peak in the β-γ fraction but did not show nephrotic syndrome, cast nephropathy or direct damage to the tubules might have been the leading cause of her renal dysfunction. A decrease in sFLC levels is reportedly associated with improvement of renal function in patients with MM [1,15,21]. This suggests that reducing sFLC levels through effective treatment for MM could directly improve renal function in these patients. The previous two IgD-MM cases that successfully withdrew from hemodialysis showed low sFLC levels [6,7], however, the present case exhibited higher sFLC levels. Thus, improvement in renal function may be dependent on treatment response rather than on sFLC levels. Bortezomib-based treatment for MM is expected to have not only an indirect effect on improving renal function by reducing sFLC production, but also a direct effect on proximal tubular inflammation via the suppression of nuclear factor-κB [1,20].

In conclusion, our patient with IgD-MM was successfully withdrawn from hemodialysis using bortezomib-based chemotherapy. Younger age and early initiation of bortezomib-based chemotherapy were identified as predictors of a successful withdrawal from hemodialysis.

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