Plasma exchange combined with bortezomib-based chemotherapy is effective for early renal recovery in a patient with IgD- λ type multiple myeloma

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Abstract

The immunoglobulin (Ig) D type is a rare variant of multiple myeloma (MM), that accounts for 1–2% of all cases. Compared to the more common types of MM, IgD MM is known to have more severe symptoms at presentation, and a poorer prognosis. A woman was admitted to our hospital for severe acute kidney disease and disorder (AKD) and back pain, and was started on hemodialysis. The renal biopsy revealed light chain cast nephropathy. She was diagnosed with IgD- λ MM based on Bence-Jones protein expression and high IgD serum levels, and started bortezomib therapy with plasma exchange (PE). After three sessions of PE, the serum free light chain levels decreased by 92%, and she was withdrawn from dialysis. The patient underwent autologous transplantation and is still in remission, demonstrating the benefits of a bortezomib-based regimen in combination with PE for IgD MM with AKD.

Keywords IgD-Multiple myeloma · Plasma exchange · Renal recovery · Acute kidney disease and disorder

Introduction

Multiple myeloma (MM), a malignant hematopoietic disease featuring clonal expansion of plasma cells in the bone marrow, is often accompanied by extensive skeletal destruction and the production of monoclonal immunoglobulins (Ig). The kidneys are the most frequently affected organs, and light chain cast nephropathy is the leading cause of renal damage. Renal failure, particularly that requiring continuous dialysis therapy, is a strong predictive factor for poor survival in patients with MM. In recent years, novel anti-myeloma agents such as bortezomib have dramatically improved renal outcomes and survival in patients with MM.

IgD MM, a rare variant of the disease, is characterized by an aggressive course and poor prognosis [1–3]. Here, we present a case of IgD MM and severe acute kidney disease and disorder (AKD) requiring dialysis. The AKD improved following short-term treatment with plasma exchange (PE) in combination with bortezomib-based chemotherapy, and the patient was withdrawn from dialysis.

Case report

A 53-year-old Japanese woman was admitted to our hospital with malaise, anorexia, and severe renal insufficiency. The patient had been otherwise healthy until 2 months before admission, when she began to experience back pain. She had no medical history, including that of kidney disease, and her creatinine level at the last medical check-up performed 6 months before admission, was within normal limits. After examination at a local clinic, she was prescribed some antacids and non-steroidal anti-inflammatory drugs (NSAIDs). On the day of admission, she visited another hospital owing to persistent malaise and anorexia, where her serum creatinine level was found to be 23 mg/dL; she was then transferred

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to our hospital. The parameters on physical examination were as follows: body temperature: 36.8 °C, blood pressure: 142/90 mmHg, pulse: 133 beats/min and regular, and body weight: 54.5 kg, indicating a 6 kg loss during the past 2 months. The remaining results were unremarkable, except for bilateral leg edema. Laboratory tests revealed the following results: hemoglobin: 10.3 g/dL, serum blood urea nitrogen: 182 mg/dL, creatinine: 23.3 mg/dL, serum sodium: 131 mEq/L, chloride: 86 mEq/L, phosphorus: 12.1 mg/dL, and blood calcium: 9.5 mg/dL (Table 1). Urine analysis showed mild proteinuria at 1.23 g/gCr, without hematuria. Although she tested positive for urine Bence-Jones protein (BJP), serum immune electrophoresis did not show M-proteins. Computed tomography of the abdomen and pelvis did not demonstrate findings indicative of hydronephrosis or parenchymal atrophic changes in either kidney (Fig. 1a). Bone analysis revealed multiple osteolytic lesions in the right humerus, right scapula, femur, and ilium, as well as in the thoracic vertebrae (Fig. 1b, c). Volume resuscitation was initiated promptly, with no response. She was started on hemodialysis on the second day, and underwent renal biopsy on the fourth. Thirty glomeruli were sampled; one was globally sclerosed, and the others showed no significant pathological alterations (Fig. 2a). However, 20% of the samples showed interstitial fibrosis and tubular atrophy (Fig. 2b). Casts, that were negative on periodic-acid Schiff staining were frequently observed within the lumen of the distal tubules (Fig. 2c). The casts were fractured, eosinophilic (hematoxylin and eosin staining), and often contained adherent neutrophils (Fig. 2d). A mean of 30 casts per ten fields was detected at a magnification of 200×. Immunofluorescent staining revealed that the casts were only positive for the lambda (λ), and not the kappa (κ) light chains (Fig. 2e, f). Collectively, these findings were consistent with those of light chain cast nephropathy. The additional laboratory test results were as follows: serum IgD: 330 mg/dL (reference, < 9.0 mg/dL), free κ light chain: 19.0 mg/L (3.3–19.4 mg/L), free λ light chain: 2500 mg/L (5.7–26.3 mg/L), and free κ : λ ratio: 0.01 (0.3–1.7). Bone marrow biopsy performed on day 12 of hospitalization revealed that approximately 70% of the constituent cells were coated with IgD and were λ -positive (Fig. 3). Based on these findings, the patient was diagnosed with IgD- λ type MM complicated with light chain cast nephropathy.

Selective PE using a plasma separator (Evacure™, Kawaumi Laboratories, INC., Tokyo, Japan) and chemotherapy (bortezomib 1.3 mg/m² weekly and dexamethasone 20 mg/body twice a week as one cycle) were started on day 19 and day 20 of hospitalization, respectively. PE was performed using 1.5 plasma volume albumin as replacement fluid once a week, to reduce the serum free λ chain (sFLC) level by 500 mg/L (Fig. 4). Chemotherapy helped reduce the sFLC level before each PE session; PE further decreased the sFLC

level by 50–60%. PE was completed on day 33 of hospitalization after three sessions, as the sFLC level before the third session was 251 mg/L. Her creatinine level also decreased simultaneously. She was finally withdrawn from dialysis on day 34 of hospitalization.

She then underwent autologous transplantation with a complete response and full renal recovery, with an estimated glomerular filtration rate of 65–70 mL/min, and is currently in complete remission with normal renal function.

Discussion

In this report, we described a case of IgD MM with severe AKD, characterized by light chain cast nephropathy. Complete recovery of renal function was achieved following bortezomib-based chemotherapy combined with PE.

Owing to the rarity of IgD MM, clinical descriptions are mostly obtained from isolated case series or limited numbers of cohort studies [2]. IgD MM is typically diagnosed at an advanced clinical stage, and before the era of novel agents as bortezomib, had an aggressive course with a poorer prognosis than other common variants of MM, such as IgG, IgA, and light chain types [1, 3–5]. Our patient had also presented with stage III (International Staging System) disease [6].

BJP is detected in 60–90% of IgD MM cases with AKD [3], and renal failure is more common in IgD MM than in other major types the condition [3, 7]. In conjunction with the bias for the λ chain and a high number of somatic hypermutations in IgD MM, the unique biology of the light chain produced in IgD MM may lead to renal disease, however, this remains to be clarified.

In our patient, renal biopsy revealed extensive tubular cast formation, mild tubular atrophy, and interstitial fibrosis. While a few studies have demonstrated the prognostic value of renal pathology for light chain cast nephropathy, tubular atrophy, interstitial inflammation, fibrosis, and number of tubular casts have been reported to be prognostic factors for renal recovery [8, 9]. In a series of 70 patients with MM and cast nephropathy, more than 20 casts per ten fields at a magnification of 200× was a significant prognostic indicator of poor renal recovery [9]. Our patient had a mean of 30 casts per ten fields, which was not indicative of a favorable renal outcome. Nevertheless, the patient showed early renal recovery. Possible explanations for this outcome include: (a) a relatively mild degree of tubular atrophy and interstitial fibrosis involving about 20% of the tubulointerstitial area, (b) the presence of other reversible precipitating factors, such as hypovolemia and the administration of NSAIDs, and (c) most importantly, a rapid reduction in the sFLC level. A recent study showed that a 60% reduction in the sFLC level by day 21 was associated with renal recovery in 80% of patients with light chain cast nephropathy [10]. Furthermore,

Table 1 Laboratory data on admission

Variable	Reference range	Results
Blood		
Hemoglobin (g/dL)	11.6–14.8	10.3
Hematocrit (%)	35.1–44.4	28.1
White-cell count (per mm ³)	3300–8600	9300
Differential count (%)		
Neutrophils	43.0–79.0	77.4
Lymphocytes	15.0–47.0	12.1
Monocytes	3.0–10.0	10.2
Eosinophils	1.0–5.0	0.2
Basophils	0.1	0.1
Platelet count (10 ³ per mm ³)	158–348	163
Reticulocytes (%)	0.5–1.8	1.1
Aspartate aminotransferase (U/L)	13–30	7
Alanine aminotransferase (U/L)	7–23	13
Lactate dehydrogenase (U/L)	124–222	199
Cholinesterase (U/L)	201–421	305
Total bilirubin (mg/dL)	0.4–1.5	0.2
Alkaline phosphatase (U/L)	106–322	247
γ -Glutamyl transpeptidase (U/L)	9–32	17
Total protein (g/dL)	6.6–8.1	7.2
Creatine kinase (U/L)	41–153	153
Albumin (g/dL)	4.1–5.1	4.1
Urea nitrogen (mg/dL)	8–20	182
Creatinine (mg/dL)	0.46–0.79	23.2
Uric acid (mg/dL)	2.6–5.5	12.9
β 2-Microglobulin (mg/L)	0.8–2.0	27.9
Sodium (mmol/L)	138–145	131
Potassium (mmol/L)	3.6–4.8	5.0
Chloride (mmol/L)	101–108	86
Calcium (mg/dL)	8.8–10.1	9.5
Phosphorus (mg/dL)	2.7–4.8	12.1
Magnesium (mg/dL)	1.8–2.6	2.9
Iron (μ g/dL)	40–188	153
Unsaturated iron binding capacity (μ g/dL)	150–280	62
Ferritin (ng/mL)	3–120	1045
Triglyceride (mg/dL)	30–149	154
HDL cholesterol (mg/dL)	40–103	77
LDL cholesterol (mg/dL)	65–139	169
Glucose (mg/dL)	73–199	112
Hemoglobin A1c (%)	4.9–6.0	6.3
C-reactive protein (mg/dL)	– 0.14	0.77
Brain natriuretic peptide (pg/mL)	– 18.4	12.5
Rheumatoid Factor (IU/mL)	– 15.0	3.0
Immunoglobulins (mg/dL)		
IgG	861–1747	479
IgA	93–393	10
IgM	50–269	5
IgD	– 9.0	330
C3 (mg/dL)	73–138	83
C4 (mg/dL)	11–31	39
Antiproteinase 3 antineutrophil Cytoplasmic antibody (U/mL)	– 3.5	1.0

Table 1 (continued)

Variable	Reference range	Results
Antimyeloperoxidase antineutrophil Cytoplasmic antibody (U/mL)	– 3.5	1.0
Antinuclear antibodies	– 20.0	5.0
Parathyroid hormone (pg/mL)	10–65	226
Cryoglobulin		Negative
Soluble interleukin-2 receptor (U/mL)	145–519	1790
Prothrombin time (%)	70–	100
Activated partial thromboplastin time (seconds)	24.0–36.0	24.2
Fibrinogen (mg/dL)	150–400	522
Free kappa light chain (mg/L)	3.3–19.4	19.0
Free lambda light chain (mg/L)	5.7–26.3	2500
Free kappa:lambda ratio	0.3–1.7	0.01
Venous blood gases		
pH		7.248
Carbon dioxide (mmHg)		29.8
HCO ₃ [–] (mEq/L)		13.0
Urine		
pH		6.0
Specific gravity		1.008
Protein		1 +
Glucose		–
Ketones		–
Blood		–
Sodium (mmol/L)		69
Creatinine (mg/dL)		76.37
Total protein (mg/dL)		94
Ratio of total protein (in mg) to Creatinine (in mg)	< 0.2	1.23
β2-Microglobulin (μg/L)		29,637
Bence-Jones Protein		Positive

Fig. 1 CT and MRI findings. **a** CT showing bilateral renal enlargement; **b** MRI showing a T1-weighted image of a fracture in the thoracic vertebrae (arrow), and **c** CT showing osteolytic lesions in the right ilium (arrowheads). *CT* computed tomography, *MRI* magnetic resonance imaging

a predialysis sFLC level < 500 mg/L after the first chemotherapy cycle has been shown to be an independent predictive factor for hemodialysis independence at 12 months [11].

Therefore, early renal recovery in our case was most likely to be related to the rapid reduction in sFLC levels.

Fig. 2 Renal biopsy findings. Trichrome staining of the **a** glomerulus showing no widening of the mesangial area or thickening of the glomerular capillary wall, $\times 200$, and **b** casts showing fractures in the distal tubules surrounded by cellular infiltration, edema, and fibrosis in the interstitium; $\times 100$. Adjacent sections showing **c** PAS-negative

and **d** and HE-positive fragments in the casts; $\times 400$. Immunofluorescence showing that most of the casts are positive for **e** λ light chains, but not for **f** κ light chains, $\times 200$ PAS periodic-acid Schiff, HE hematoxylin and eosin

The introduction of bortezomib-based chemotherapy has dramatically improved renal outcomes and survival in patients with light chain cast nephropathy [12], and is currently the first-line therapy for MM and renal failure. In contrast, the efficacy of the extracorporeal method, i.e., PE or the use of a high-cutoff dialyzer for renal recovery in

cases of light chain cast nephropathy, remains to be established. In the setting of severe renal insufficiency requiring renal replacement therapy, the clearance of sFLC from the circulation is remarkably impaired. Thus, the removal of sFLC by the extracorporeal method should reduce sFLC rapidly. Two relatively large randomized controlled trials were

Fig. 3 Bone marrow biopsy findings. **a** Hematoxylin and eosin staining showing an abundance of atypical plasmacytoid cells in the bone marrow; $\times 200$. Immunostaining showing **b** expression of IgD and

restricted expression of the λ chain in most plasmacytoid cells, $\times 200$. IgD immunoglobulin D

Fig. 4 Clinical course of our case. The line graph in blue shows the trends in creatinine levels. The dark brown bars depict sFLC levels, and the light brown bars illustrate sFLC levels after each PE session.

Gray bars showing daily urine volumes. *Cr* creatinine, *sFLC* serum lambda free light chain, *HD* hemodialysis, *Bor* bortezomib, *Dex* dexamethasone, *RBx* renal biopsy, *PE* plasma exchange

conducted recently to address the controversies regarding the effectiveness of the extracorporeal method in patients with newly diagnosed MM, severe AKD requiring hemodialysis, and biopsy-proven light chain cast nephropathy [11, 13, 14]. The Multiple Myeloma and Renal Failure Due to Cast Nephropathy (MYRE) trial showed higher rates of hemodialysis independence at 6 and 12 months in the high-cutoff dialysis group; however, the trial did not demonstrate

statistical significance at the primary endpoint (3 months) [11]. In contrast, the European Trial of Free Light Chain Removal by Extended Dialysis (EuLITE) showed no benefits with high-cutoff dialysis during their follow-up period (2 years) [14]. The difference in these results may be partly explained by differences in their chemotherapeutic regimens, EuLITE used a triplet regimen (bortezomib, doxorubicin, and dexamethasone), whereas MYRE selected a less

intensive doublet regimen (bortezomib and dexamethasone) reinforced by cyclophosphamide after 3 months, if indicated. Indeed, the more intensive chemotherapeutic regimen in EuLITE was, accompanied by a higher dialysis independence rate after 90 days in both groups (56% in the high-cutoff hemodialysis group and 51% in the standard high-flux hemodialysis group) compared to the MYRE trial (41.3% in the high-cutoff hemodialysis group and 33.3% in the conventional hemodialysis group). Thus, high-cutoff dialysis may be expected to have a greater impact on reducing sFLC in cases receiving a less intensive doublet regimen.

High-cutoff hemodialysis is not currently available in Japan. PE is an alternative extracorporeal method for sFLC removal; however, no randomized control trials have evaluated the efficacy of PE in combination with bortezomib for light chain cast nephropathy with severe AKD. The frequency of PE in our case (once a week) was lower than that of other reports (5–7 exchanges within 7–10 days) from other countries [15]. This was primarily owing to the regulations of the national health insurance system, which restrict the frequency of PE to once a week. Nevertheless, reviewing the trend of sFLC levels, the sFLC levels decreased by 50–60% after each session of PE (Fig. 4; this is consistent with the findings of previous reports regarding PE treatments. Finally, the sFLC levels after 14 days of therapy were < 500 mg/L (92% reduction). Therefore, PE undoubtedly aided in the rapid reduction of sFLC levels, and could contribute to early renal recovery.

A recent cohort study revealed that, in the era of novel chemotherapeutic agents such as bortezomib, the prognosis of IgD MM is comparable to that of other common types of MM; however, its presentation is severe, and is more frequently accompanied by renal failure [16]. However, the renal outcomes of IgD myeloma cast nephropathy (MCN), particularly that requiring dialysis, are not fully understood. Further studies are needed to examine and confirm the effectiveness of PE in combination with a bortezomib-based regimen in achieving rapid improvement in cases of IgD MCN with severe AKD, requiring dialysis.

Conclusions

PE combined with a bortezomib-based regimen may effectively reduce sFLC levels in patients with IgD-MM and AKD; this facilitates early renal recovery and withdrawal from dialysis.

Compliance with ethical standards

Conflict of interest All the authors have declared no competing interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee at which the studies were conducted and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from the patient included in the study.

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