【 CASE REPORT 】

Vancomycin Intoxication and Cefepime-induced Encephalopathy Treated by Abdominal Drainage of Massive Ascites in Addition to Online Hemodiafiltration

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Abstract:
A patient with recurrent plasmacytoma with massive ascites exhibited vancomycin intoxication and cefepime-induced encephalopathy due to renal dysfunction. The ascitic accumulation of these drugs was suspected because of the refractory intoxicated state. To remove these drugs that had accumulated in the blood and ascites, abdominal drainage was performed in addition to online hemodiafiltration. If patients with renal dysfunction and massive ascites develop vancomycin intoxication and cefepime-induced encephalopathy that cannot be improved by drug discontinuation, physicians should suspect ascitic accumulation and evaluate the ascitic concentration. Furthermore, if a high accumulation in massive ascites occurs, physicians should perform abdominal drainage along with blood purification.

Key words: AKI, vancomycin intoxication, cefepime-induced encephalopathy, abdominal drainage, online hemodiafiltration

Introduction

Antibiotics are either eliminated in active form through the kidney or metabolized through the liver. Therefore, it is necessary to adjust the antibiotic dosage and frequency of administration in patients with renal or hepatic failure (1, 2). If symptoms of intoxication due to antibiotic overdose are suspected by physicians, they should monitor the blood concentration, discontinue the suspected drugs, administer antidotes, or perform blood purification (3, 4). However, to our knowledge, there have been no reports focusing on the transfer and accumulation of suspected drugs into body fluids other than blood.

We herein report a case of plasmacytoma with massive ascites where vancomycin (VCM) and cefepime (CFPM) were administered as acute pyelonephritis developed along with bacteremia during chemotherapy, and subsequently, VCM intoxication and CFPM-induced encephalopathy (CIE)

occurred due to renal dysfunction, resulting in the accumulation of these drugs in ascites.

Case Report

A 55-year-old man, with a history of plasmacytoma, was admitted to the hematology department of our hospital due to its recurrence. He had initially complained of a mass at his anterior chest a year and a half before. Based on the biopsy of the chest lesion, he was diagnosed with plasmacytoma. Positron emission tomography-computed tomography (PET-CT) revealed an increased ^{18}F-fluorodeoxyglucose uptake in his anterior chest, upper thoracic spine, lumbar spine, sacrum, and both scapulae. The spinal lesions caused lower limb paralysis and bladder disturbance, which were difficult to improve with spinal surgery. Several types of chemotherapy (two cycles of vincristine, doxorubicin, and dexamethasone; two cycles of bortezomib, lenalidomide, and dexamethasone; and 11 cycles of pomalidomide, cyclophos-
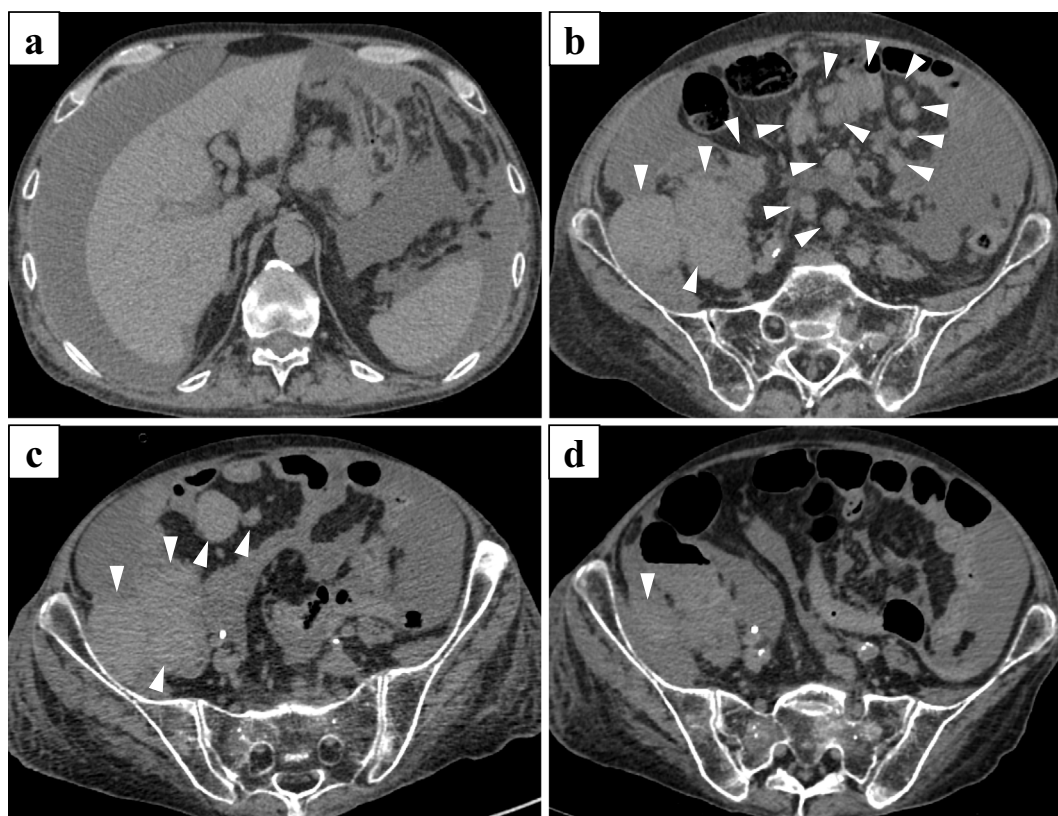
Figure 1. CT imaging. (a, b) Abdominal CT captured on admission revealed massive ascites with a low Hounsfield unit value and multiple intraperitoneal lesions (white arrows). (c, d) Follow-up CT revealed shrinkage of the lesions (white arrows) (c: day 40, d: day 54).

phamide, and dexamethasone) controlled exacerbation of plasmacytoma, but lower limb paralysis and bladder disturbance continued.

The patient visited our hospital with a new complaint of abdominal distention. Computed tomography (CT) revealed massive ascites with a low Hounsfield unit value and multiple intraperitoneal lesions (Fig. 1a, b). The cytological examination of ascites revealed atypical plasma cells, suggesting recurrence of plasmacytoma.

On day 2 of admission, daratumumab, bortezomib, and dexamethasone were initiated; however, he developed acute pyelonephritis with bacteremia on day 8, and ceftazidime (CAZ) was initiated. His body temperature decreased from day 9 to day 10; however, it increased again on day 11, and antibiotics escalation (from CAZ to CFPM) was performed. As the causative bacteria, *Klebsiella pneumoniae*, was proven to be sensitive to cefazolin (CEZ), antibiotics de-escalation (from CFPM to CEZ) was performed on day 16, but his body temperature increased again on day 21 and did not decrease despite repeated escalation of antibiotics (from CEZ to CFPM). Based on urinary culture on day 21, urinary tract infection due to *Enterococcus faecium* was suspected, so VCM was added to CFPM on day 24.

Follow-up CT to evaluate the state of plasmacytoma demonstrated progressive disease, so as a stronger regimen, carfilzomib, lenalidomide, and dexamethasone were initiated on day 25. On day 26, acute kidney injury (AKI) was observed.

On day 29, aggravation of AKI and high serum levels of VCM were observed, so VCM was discontinued, and infusion of crystalloid was initiated. On day 30, consciousness disorder was observed, and the patient was referred to the nephrology department with suspicion of uremia.

His body height was 176.4 cm, body weight 61.7 kg, blood pressure 100/62 mmHg, heart rate 80 beats/min, body temperature 37.2°C, respiratory rate 16 beats/min, blood oxygen saturation level 98% with oxygen administered at 2 L/min, and Glasgow Coma Scale E4V4M5. A physical examination revealed abdominal distention; however, an examination of the other parts of the body was unremarkable. No lung rales or heart murmurs were detected on chest auscultation. Laboratory findings revealed renal dysfunction, pancytopenia, hypoalbuminemia, high serum levels of VCM, and high urinary levels of β_2-microglobulin (β_2MG) and N-acetyl-beta-D-glucosaminidase (NAG) (Table). The possibility of prerenal and postrenal AKI was considered limited as a cause of renal dysfunction, since laboratory findings did not show a low fractional excretion of sodium or urea nitrogen; echocardiography did not reveal collapse of the inferior vena cava (IVC), left ventricular asynergy, or valvular dysfunction; and abdominal CT revealed no evidence of expansion of the renal pelvises. The possibility of stroke, meningoencephalitis, plasmacytoma invasion to the central nervous system, uncontrolled urinary tract infection, uremia, and thrombotic thrombocytopenic purpura (TTP) were consid-

Table.   Laboratory Findings on the Patient Referral to the Nephrology Department.

Blood cell count		Coagulation		Venous blood gas	
WBC	1,860 /μL	PT-INR	1.27	pH	7.39
RBC	2.48×10⁶ /μL	APTT	35.7 s	pCO₂	40.1 mmHg
Hb	8.1 g/dL	Fibrinogen	396 mg/dL	pO₂	74.1 mmHg
Hct	24.0 %	D-dimer	0.79 μg/mL	HCO₃⁻	23.9 mmol/L
Plt	3.3×10⁴ /μL	Drug monitoring		Base excess	-0.9 mmol/L
Blood chemistry		VCM levels	47.1 μg/mL	Anion gap	7.8 mmol/L
CRP	4.44 mg/dL	Immunochemistry		Lactate	0.69 mmol/L
TP	3.4 g/dL	IgG	213 mg/dL		
Alb	1.6 g/dL	IgA	21 mg/dL	Urinalysis	
AST	29 U/L	IgM	3 mg/dL	pH	1.008
ALT	14 U/L	IgG4	8.9 mg/dL	Protein	(1+)
LDH	276 U/L	Free light chain κ	6.4 mg/dL		4.17 g/gCre
T-Bil	0.3 mg/dL	Free light chain λ	1,044 mg/dL	Occult blood	(1+)
BUN	69.4 mg/dL	Bence-Jones protein	Positive	RBC	5-9 /HPF
Cre	3.24 mg/dL	ADAMTS13-activity	49 %	WBC	5-9 /HPF
eGFR	16.97 mL/min	ANA	Less than ×40 titer	Granular casts	few/LPF
Na	128 mEq/L	MPO-ANCA	Negative	Dysmorphic RBC	Negative
K	5.0 mEq/L	PR3-ANCA	Negative	UN	182 mg/dL
Cl	97 mEq/L	Anti-GBM antibody	Negative	Na	58 mEq/L
Ca	10.1 mg/dL	ACE	16.1 IU/L	Cl	69 mEq/L
Mg	3.7 mg/dL	EBV-VCA IgM	Less than ×10 titer	Cre	15.4 mg/dL
iP	5.2 mg/dL	EBV-VCA IgG	×40 titer	NAG	141.4 U/L
UA	5.3 mg/dL	EBNA	×20 titer	β₂MG	53,948 μg/L
Haptoglobin	97 mg/dL	CMV antigenemia	Positive	Bence-Jones protein	Positive
β₂MG	38.1 mg/L	NH₃	22 μg/dL		

eGFR: estimated glomerular filtration rate, β₂MG: β₂-microglobulin, VCM: vancomycin, ADAMTS13: a disintegrin and metalloproteinase with thrombospondin motifs 13, ANA: antinuclear antibody, MPO-ANCA: myeloperoxidase anti-neutrophil cytoplasmic antibody, PR3-ANCA: proteinase 3 anti-neutrophil cytoplasmic antibody, GBM: glomerular basement membrane, ACE: angiotensin-converting enzyme, EBV: Epstein-Barr virus, VCA: virus capsid antigen, EBNA: Epstein-Barr virus nuclear antigen, CMV: cytomegalovirus, NAG: N-acetyl-beta-D-glucosaminidase

ered limited as a cause of consciousness disorder, since head CT and magnetic resonance imaging (MRI) revealed no evidence of intracranial lesions, an examination of the cerebrospinal fluid (CSF) revealed no evidence of cell proliferation or atypical cells, a sufficient amount of antibiotics effective against the causative bacteria had been administered, and the laboratory findings did not show high anion gap metabolic acidosis, decreased serum haptoglobin levels, or decreased activity of a disintegrin and metalloproteinase with thrombospondin motifs 13 (ADAMTS13) (Table). It was therefore suspected that AKI had developed due to myeloma kidney and VCM intoxication, since the laboratory findings showed high serum levels of free light chains and VCM and high urinary levels of β₂MG and NAG. Simultaneously, it was also suspected that consciousness disorder might have developed due to CIE, since a large amount of CFPM had been administered in the presence of renal dysfunction. Indeed, electroencephalography (EEG) showed triphasic waves but not epileptic waves, consistent with drug-induced encephalopathy.

To improve his VCM intoxication and CIE, VCM and CFPM were discontinued on day 29; however, there was no trend of decreased serum levels of VCM or consciousness recovery. Thus, on day 32, online hemodiafiltration (OHDF) was conducted to remove these drugs. An ascites examination revealed high ascitic concentrations of VCM, suggesting a refractory intoxicated state of the patient due to the accumulation of VCM and CFPM in massive ascites.

To remove these drugs that had accumulated in the blood and ascites, abdominal drainage was also performed in addition to OHDF. After performing OHDF thrice and abdominal drainage twice, the serum and ascitic levels of VCM decreased to 10-15 μg/mL. Every session was pre-dilution and the volume of substitutes was 72 L/session in OHDF. Furthermore, the consciousness of the patient recovered (from E4V4M5 on day 30 to E4V5M6 on day 37), and triphasic waves captured on the first EEG disappeared in the second EEG on day 40. Follow-up CT demonstrated progressive disease (Fig. 1c), so a stronger regimen of bortezomib, doxorubicin, and intermediate-dose dexamethasone was introduced on day 40.

Despite the successful removal of VCM, aggravated renal dysfunction and low urine output continued, resulting in hypoxia due to pleural effusion unresponsive to diuretic therapy. On day 40, thrice weekly sessions of hemodialysis (HD) were introduced. The patient developed cytomegalovirus (CMV) viremia on day 43, so ganciclovir was administered until negative conversion of CMV antigenemia. A significant improvement in the renal function was noted from day 47, and HD was discontinued on day 52. Follow-up CT
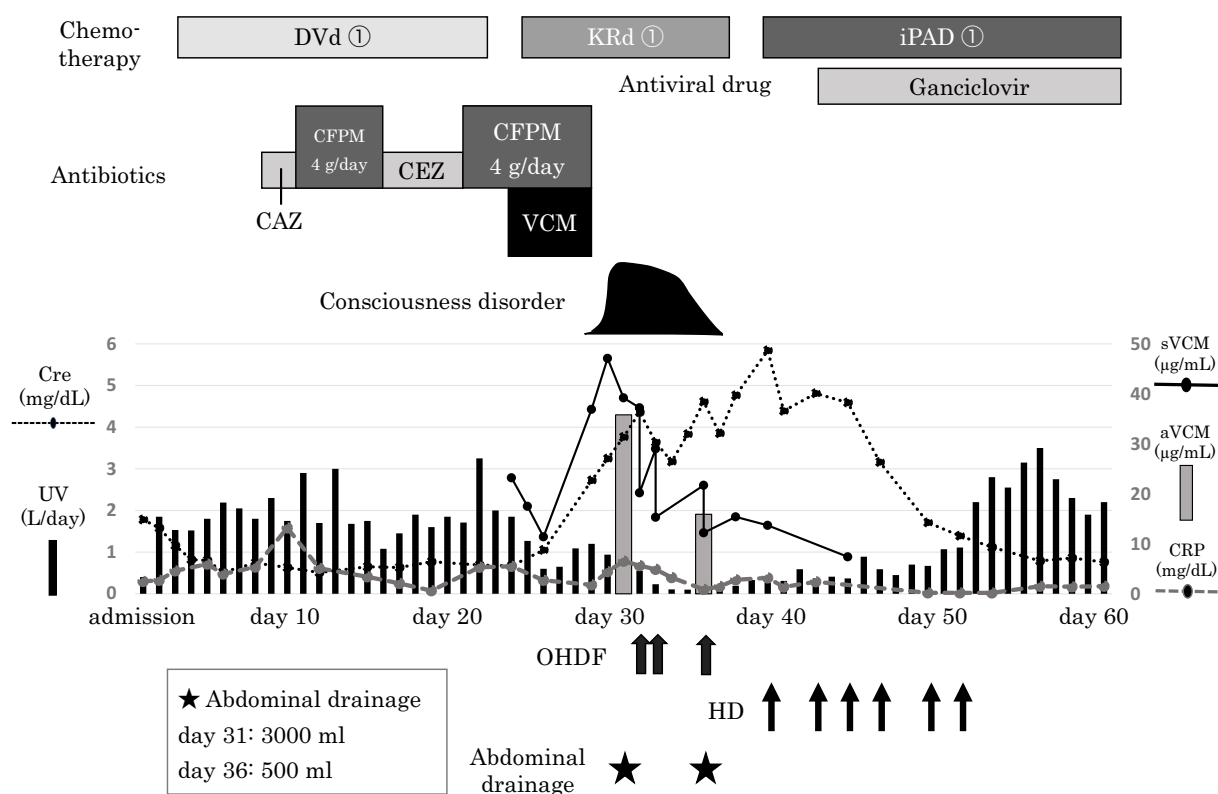
Figure 2. **The clinical course. Cre: serum creatinine level, UV: urine volume, CAZ: ceftazidime, CFPM: cefepime, CEZ: cefazolin, VCM: vancomycin, HD: hemodialysis, OHDF: online hemodiafiltration, DVd: daratumumab, bortezomib, and dexamethasone, KRd: carfilzomib, lenalidomide, and dexamethasone, iPAD: bortezomib, doxorubicin, and intermediate-dose dexamethasone, sVCM: serum concentration of vancomycin, aVCM: ascitic concentration of vancomycin**

captured on day 54 demonstrated a partial response (Fig. 1d), and blood tests revealed a decrease in the amount of free light chains, suggesting that the new regimen initiated on day 40 was effective against recurrent plasmacytoma. Therefore, the next cycle of the regimen was initiated on day 65.

A schematic outline of the clinical course is shown in Fig. 2.

Discussion

We herein report a patient with recurrent plasmacytoma to whom VCM and CFPM were administered because of the development of acute pyelonephritis with bacteremia during chemotherapy, and subsequently VCM intoxication and CIE occurred in the presence of renal dysfunction. Abdominal drainage was performed in addition to OHDF, as the possibility of accumulation of these drugs in massive ascites was suspected, leading to the successful treatment of VCM intoxication and CIE. We searched for the phrases "vancomycin/poisoning" [MeSH terms], "cefepime/adverse effects" [MeSH terms] in PubMed, and, to our knowledge, this is the first report to describe the transfer and accumulation of these drugs into ascites in a patient with VCM intoxication and CIE.

The pharmacokinetic characteristics of VCM are an ap-

proximately 80-90% excretion via urine, with a volume of distribution (Vd) of approximately 0.4-1.0 L/kg. In contrast, approximately 80% of CFPM is excreted via the urine, with a Vd of approximately 0.2 L/kg (5-7). VCM and CFPM were presumed to have a high transferability to ascites, since the ascitic concentrations of these drugs were increased after intravenous administration in patients with peritoneal dialysis and abdominal surgery (8-10), and the intravenous administration of these drugs was effective against peritonitis in peritoneal dialysis patients and spontaneous bacterial peritonitis in liver cirrhosis patients (11, 12). In the present case, a large amount of newly developed ascites led to the diagnosis of recurrent plasmacytoma, so the patient was at risk of the ascitic accumulation of VCM and CFPM due to the high transferability to ascites. In addition, the risk of ascitic accumulation was increased because of the low urinary excretion of VCM and CFPM due to AKI. An ascites examination resulted in the early detection of the ascitic accumulation of these drugs.

The removal efficiency of a drug by HD mainly depends on its molecular weight, protein binding, Vd, and water solubility. Drugs satisfying the pharmacokinetic properties of a low molecular weight, low protein binding, low Vd, and high water solubility have a high removal efficiency by HD, while those without any of these properties have a low removal efficiency by HD. The removal of drugs less dialys-

able in HD requires the administration of antidotes or other techniques of blood purification, such as hemodiafiltration, plasma exchange, or plasma absorption (13). VCM has a relatively high molecular weight of 1,450 g/mol, protein binding of approximately 10-50%, low Vd of approximately 0.4-1.0 L/kg, and high water solubility, while CFPM has a relatively low molecular weight of 571.5 g/mol, protein binding of approximately 16-19%, low Vd of approximately 0.2 L/kg, and high water solubility (5-7, 14). VCM was estimated to have a lower removal efficiency in HD than CFPM, as its molecular weight was higher than that of CFPM, although both drugs have low protein binding, low Vd, and high water solubility. In general, OHDF is more effective than HD at removing drugs of medium molecular weight. As reported previously, OHDF was effective in removing VCM (15); OHDF was therefore performed in the present case to remove both VCM and CFPM. However, an ascites examination suggested the accumulation of these drugs in massive ascites. The intoxicated state of the patient was presumed to be refractory due to the blood and ascitic accumulation, abdominal drainage was therefore performed in addition to OHDF to remove these drugs efficiently, resulting in the successful improvement of VCM intoxication and CIE.

In this case, myeloma kidney and drug-induced nephropathy were suspected as the primary causes of AKI and CIE as the primary cause of consciousness disorder. Prerenal and postrenal AKI were ruled out as the causes of AKI, since urine tests did not show a low fractional excretion of sodium or urea nitrogen, echocardiography did not reveal the collapse of the IVC, left ventricular asynergy, or valvular dysfunction, and abdominal CT revealed no evidence of expansion of the renal pelvises. High urinary levels of β_2MG and NAG suggested the presence of tubulointerstitial damage of the kidneys. Laboratory findings did not support the possibility of systemic lupus erythematosus, Sjögren's syndrome, sarcoidosis, IgG4-related disease, ANCA-associated vasculitis, anti-glomerular basement membrane disease, or hyperuricemia. Uncontrolled urinary tract infection was also ruled out, as a sufficient amount of antibiotics effective against the causative bacteria had been administered. It was finally concluded that myeloma kidney and VCM-induced nephropathy were the primary causes of AKI, as the patient developed refractory plasmacytoma with high serum levels of free light chains, and a high serum level of VCM was observed. Despite the introduction of a stronger regimen for plasmacytoma, discontinuation of VCM, OHDF, and abdominal drainage, rapidly progressive renal dysfunction was observed, resulting in the introduction of HD on day 40. The low urine output initially continued; however, the renal function started to improve on day 47, and HD was discontinued on day 52.

On the other hand, the laboratory findings did not support the possibility of abnormal blood sugar levels, electrolyte imbalance, hyperammonemia, or TTP as a cause of consciousness disorder. Imaging findings, the examination of

the CSF, and the EEG did not support the possibility of stroke, meningoencephalitis, plasmacytoma invasion to the central nervous system, or epilepsy. Uremia was also ruled out as well, since consciousness disorder remained for several days even after the improvement of azotemia by OHDF. CIE was suspected as the primary cause of consciousness disorder, as a large amount of CFPM had been administered in the presence of renal dysfunction. Discontinuation of CFPM, OHDF, and abdominal drainage were performed to improve CIE, leading to an improvement in consciousness disorder.

Several differences were noted between a typical case of CIE and that observed in this case. The clinical characteristics of CIE are a median onset of approximately 4-5 days after CFPM initiation, improvement of neurotoxicity symptoms several days after treatment, including blood purification, and renal dysfunction (16, 17). In contrast, the present case had a relatively long period from CFPM initiation (day 21) to the onset of CIE (day 30) and a relatively long period from CFPM discontinuation (day 29) to the improvement in consciousness disorder (day 37), atypical as a clinical course of CIE. The atypical course of CIE in this case may have been due to massive ascites acting as a kind of "buffer agent". CFPM concentrations in the CSF might not increase easily due to its high transferability into ascites; however, once the concentration in the CSF rose to the degree that the patient developed CIE, the concentration might have remained unchanged due to the marked accumulation in ascites, resulting in prolonged CIE.

In this case report, four clinical problems remained to be discussed. First, there was no direct proof of CIE or the CFPM accumulation in ascites, as the CFPM concentrations in the blood, ascites, and CSF could not be examined due to the lack of insurance coverage in Japan. However, the discussion concerning the pharmacokinetics of CFPM in this case is valid, since other etiologies of consciousness disorder were ruled out, the consciousness disorder and EEG findings were improved after the treatment according to CIE, CFPM had high transferability into ascites according to previous reports that ascitic concentrations of CFPM were increased after its intravenous administration in patients with peritoneal dialysis and abdominal surgery, and the administration of CFPM was effective against peritonitis in peritoneal dialysis patients and spontaneous bacterial peritonitis in liver cirrhosis patients. Second, abdominal drainage may not have been needed to improve VCM intoxication and CIE. The intoxicated state of the patient could have been treated by OHDF alone without abdominal drainage; however, more sessions of OHDF would have been required to remove these drugs that were accumulated in blood and massive ascites. Third, the definitive diagnosis of AKI was not confirmed, as performing a renal biopsy was difficult due to the low platelet count. Recurrent plasmacytoma with high serum levels of free light chains and VCM and high urinary levels of β_2MG and NAG suggested the possibility of myeloma kidney and VCM-induced nephropathy, while CMV viremia

also suggested the possibility of CMV nephropathy. Furthermore, carfilzomib-related AKI was not ruled out (18). Fourth, lenalidomide-related encephalopathy was not ruled out. Lenalidomide-related neurological and psychiatric disorders, such as headache, dizziness, tremor, peripheral neuropathy, or anxiety may occur, although consciousness disorder is a rare complication (19-27). Ischemic stroke and progressive multifocal leukoencephalopathy are reported to be lenalidomide-related encephalopathies detectable with head MRI (28, 29). Since head MRI showed no abnormal findings in this case, the possibility of lenalidomide-related encephalopathy was considered limited.

In summary, we herein report a case of recurrent plasmacytoma developing VCM intoxication and CIE due to VCM and CFPM overdose in the presence of renal dysfunction, resulting in the transfer and accumulation of these drugs into massive ascites. If patients with an impaired renal function and massive ascites develop VCM intoxication and CIE, physicians should consider the possibility of these agents' transfer and accumulation into ascites and evaluate the ascitic concentration of the suspected drugs. Furthermore, if the high accumulation of drugs in massive ascites occurs, to reduce the number of sessions of blood purification, physicians should consider performing abdominal drainage in addition to blood purification.

Informed consent was obtained from all individual participants included in the study.

The authors state that they have no Conflict of Interest (COI).

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