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CASE REPORT

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Cardiopulmonary arrest caused by nafamostat mesylate during hemodialysis

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Abstract

Dialysis-related adverse reactions can be serious and difficult to predict. In our case, nafamostat mesylate (NM) was thought to be the cause of cardiopulmonary arrest (CPA) due to NM-induced anaphylaxis but was not reflected in the allergy tests. Rare but life-threatening drawbacks occur immediately after hemodialysis initiation.

KEYWORDS

and anaphylaxis, cardiopulmonary arrest, dialysis-related adverse reactions, hemodialysis, nafamostat mesylate

1 | INTRODUCTION

Uncommon but serious adverse events may occur immediately after HD initiation.[1–3] There are many causes for this acute reaction, including materials used in dialyzers, circuits, and drugs.[3–8] We experienced a case of unpredictable CPA with rapidly progressing severe anaphylaxis without skin symptoms. Based on the clinical course, the cause of cardiopulmonary arrest was considered to be anaphylaxis caused by NM. However, the drug lymphocyte stimulation test (DLST) and basophil activation test (BAT) as allergy evaluations were negative. The discrepancy between the clinical course and the results of these allergy tests suggests that the mechanism is complex and not uniform.

2 | CASE PRESENTATION

An 82-year-old Japanese woman had been on HD in a peripheral dialysis clinic for the past 11 years because of diabetic nephropathy. She had difficulty moving due to a lumbar spine fracture. Her left chest was swollen as a result of family members holding her to help her stand. She arrived at our hospital by ambulance because she had become unconscious after returning home from the HD clinic. Upon admission to our hospital, the patient recovered consciousness. Contrast-enhanced computed tomography showed a massive intramuscular hematoma in her left pectoralis major; however, she was conservatively managed with a blood transfusion because there was no extravasation. On her second day in the hospital, her hemodynamics stabilized, and she underwent conventional HD (dialyzer: AEF-13® Asahi Kasei Corp., Japan). We used generic NM as an anticoagulant in the dialysis circuit and started at a dose of 40 mg/h. She went into cardiopulmonary arrest 7 min after the start of HD, and the total amount of NM administered was approximately 5 mg. She had no skin symptoms, such as wheals or erythema. The patient underwent airway management and chest compressions, and hemodialysis was immediately discontinued. A total of 4 mg of epinephrine was administered, and spontaneous circulation recovered 14 minutes after cardiopulmonary arrest. At that point, we could not

establish an accurate diagnosis of NM-induced anaphylactic shock. The DLST and BAT were negative (Table 1). On her fourth day in the hospital, the patient's hemodynamics stabilized again, and she underwent sustained low efficiency dialysis (SLED) (dialyzer: APS-10SA® Asahi Kasei Corp.) using the same NM as the previous time. Ten minutes after the start of the SLED, her blood pressure dropped precipitously to 60 mmHg. She had no skin reaction at this time. The SLED was discontinued immediately, and intramuscular epinephrine was administered because of the suspicion of anaphylactic shock. The total amount of NM used was less than 5 mg. Her blood pressure was maintained with isotonic sodium chloride solution, norepinephrine, and human serum albumin. After changing the anticoagulant to heparin and the dialyzer with another type of membrane, no further episodes of anaphylactic reactions were observed during subsequent HD (Table 2). Twenty days after admission, the second DLST result was negative. On the 30th hospital day, the patient died due to pneumonia.

3 | DISCUSSION

According to the previous reports, adverse reactions resulting from blood contact with the dialysis circuit and anticoagulants may occur immediately after dialysis initiation.[1–8] Based on the clinical course of our patient, NM was thought to have caused anaphylactic shock leading to cardiopulmonary arrest (CPA). Both the BAT and DLST, which are allergic auxiliary tests for NM, were negative, suggesting the existence of a complex reaction pathway. Cardiopulmonary arrest immediately after dialysis has a rapid course, and its cause and mechanism are unpredictable. Therefore, close observation is essential. Simultaneous changes in anticoagulants and dialysis circuits including dialyzer may be safe to avoid adverse reactions during the next session.

Because of the complexity of dialysis systems, composed of many different materials, it is challenging to identify substances that can cause adverse reactions. According to Tanaka et al., CPA during HD occurs at a frequency of 1.1–7.5 times per 100,000 HD sessions.[9] Several studies have reported cases of severe symptoms such as shock, hypotension, or dyspnea immediately after dialysis using PS membranes.[1–3] It has been reported that polysulfone (PS) membranes are the most common type of membrane in Japanese chronic hemodialysis patients[10] and acute dialysis reactions often occur.[1,7] It has been pointed out that bisphenol A in PS membranes and polyvinylpyrrolidone as a hydrophilic agent can alter the antigenicity of adsorbed endogenous proteins and cause hypersensitivity.[3,4,7] Cases of thrombocytopenia caused by PS membrane dialyzers have been reported,[11,12] and thrombocytopenia caused by a dialyzer, APS-15A (PS membrane), as in our case, has been reported on the US Food and Drug Administration website.[8] Chen et al. presented a case in which the allergen was suspected to be a blood tubing set or its accessory, and not a membrane material. The author expressed that if these reactions are suspected, it is imperative to stop dialysis immediately and not return blood.[6] In our case, thrombocytopenia was not observed during HD and could not be confirmed as a membrane-related adverse reaction. In addition, myocardial markers were elevated, but electrocardiographic and echocardiography did not confirm Kounis syndrome (Table 2).

To the best of our knowledge, only three cases of CPA due to the use of NM have been reported (Table 3).[13–15] One of the features that made diagnosis difficult in our case was the lack of skin findings. Historically, 80%–90% of anaphylactic events have been associated with mucocutaneous symptoms. In contrast, on the contrary, Kim et al. reported that the incidence of skin manifestations of NM-induced anaphylaxis was 29.8%.[13] Ito et al. mentioned that there is currently no effective method for predicting NM-induced allergic reactions because various mechanisms are thought to be involved.[16] Several reports have highlighted the importance of clinical suspicion, as it is difficult to predict the onset of anaphylaxis.[13,15,16]

The DLST and BAT test results were negative, although our case showed a life-threatening course of anaphylaxis. The results of these tests suggested non-IgE-mediated anaphylaxis. Previous reports of NM-induced anaphylactic shock showed a 75% positivity rate for DLST.[13–17] However, according to Oda et al., the accuracy of this test is easily affected by drug concentration, measurement time, and concomitant drug use.[17] Sugihara et al. showed that a second DLST improves diagnostic accuracy.[18] However, in our case, the second DLST did not reflect results consistent with the clinical course. BAT is a flow cytometry-based assay validated for IgE-mediated anaphylaxis. The expression of activation markers such as CD63 and CD203c on the surface of basophils was measured following stimulation with an allergen. BAT may be reliable and safe for confirming clinical suspicion,

TABLE 1 Results of blood tests for anaphylaxis

Blood tests	Measured value	
Non-specific IgE antibody levels	196 IU/ml (0–170)	
Serum complement (CH50)	<14 CH50/ml (30–45)	
DLST	Negative	(SI 139%)
BAT	Negative	
DLST (20 days after CPA)	Negative	(SI 152%)

Abbreviations: BAT, basophil activation test; DLST, drug lymphocyte stimulation test; SI, stimulation index.

TABLE 2 Anticoagulants, dialyzers, and blood tests during the course of hospitalization

Hospital day	Day 0	Day 2	Day 3	Day 5	Day 6	Day 7	Day 8	Day 11	Day 13	Day 15	Day 18	Day 20	Day 22	Day 25
Event	Admission	CPA		BP depression										Death
Type of dialysis		HD		SLED	CHDF		HD	HD	HD	HD	HD	HD	HD	HD
Anticoagulant		NM		NM	Heparin		Heparin	Heparin	Heparin	Heparin	Heparin	Heparin	Heparin	Heparin
Dialyzer		APS-15SA		AEF	UT-1100eco		FB-110Uβeco	FB-110Uβeco	FB-110Uβeco	FB-110Uβeco	FB-110Uβeco	FB-110Uβeco	FB-110Uβeco	FB-110Uβeco
Membrane		PS		PS	CTA		CTA	CTA	CTA	CTA	CTA	CTA	CTA	CTA
Blood tests		Before CPA		Before BP fall										
WBC (/mm3)	13,900	6900	13,700	15,400	12,700	11,000	10,700	8700	9100	9500	12,900	9700	10,100	7800
Eosino(%)	0.1	1	0	1	2	0	1	1	1	1	0.4	2	5	2
Neutro(%)	78.7	90	90	92	87	84	85	85	81	89	86.3	76.3	77	79
Platelet (/mm3)	24.8	20.5	23.1	24.7	20.7	19.1	20.5	23.4	28.5	28.8	21.1	19.5	22.2	28.4
CRP (mg/dL)	7.72	11.32	13.62	9.11	8.55	10.52	8.25	3.15	1.77	1.41	8.3	10.81	7.54	3.08
GOT (IU/L)	17	15	46	28	28	44	43	32	31	30	26	29	26	25
LDH (IU/L)	291	266	482	509	421	479	541	542	518	459	409	423	439	303
CK-MB (mg/dL)	26 (12%)	13.0 (7%)	88 (14%)	41 (22%)	27 (8%)									
Trop-I (ng/mL)	0.05	0.09	1.09	0.46	0.41									

Abbreviations: BP, blood pressure; CHDF, continuous hemodiafiltration; CPA, cardiopulmonary arrest; CTA, cellulose triacetate; HD, hemodialysis; NM, nafamostat mesylate; PS, polysulfone; SLED, sustained low-efficiency dialysis.

TABLE 3 Cases of cardiac arrest due to nafamostat mesilate in the literature

Cases		Age	Skin symptom	Diagnostic test			Time to CPA (minutes)	Dialysis history (years)	Prior exposure (times)	Original or Generic product
				Total IgE	DLST	BAT				
1	Kim JH[13]	75 F	Itching, urticaria	elevation	ND	Positive	50	10	multiple	NS
2	Kim HS[14]	65 M	None	elevation	ND	ND	15	5	NS	NS
3	Kato F[15]	51 M	None	ND	ND	ND	4	8	7	Original product
4	Our case	82 F	None	not elevation	negative	Negative	7	11	2	Generic medication

Abbreviations: BAT, basophil activation test; CPA, cardiopulmonary arrest; DLST, drug lymphocyte stimulation test; ND, not done; NM, Nafamostat Mesylate; NS, not stated.

eliminating the need to perform dangerous drug challenge tests in cases where no alternatives are available.[19] Although several studies have confirmed its utility in cases of sugammadex-[20] and cefazolin-induced anaphylactic shock[21] without skin symptoms, the number of cases associated with BAT remains small.

NM has often been used as an anticoagulant in hemodialysis patients with a high risk of bleeding in East Asia, especially in Japan. Maruyama reported that the anticoagulant effect of NM is strictly limited to the extracorporeal circuit because it has a biological half-life of less than 8 min,[22] and approximately 40% of the molecule is dialyzed.[23] Okuyama reported that NMs do not exhibit antigenicity,[24] but hydrolyzed NMs produce two metabolites that bind to human serum albumin and exhibit antigenicity.[15,24] The originator pharmaceutical company has an NM-specific IgE antibody measurement kit; however, pharmaceutical companies that manufacture generics do not have this kit. Therefore, when a serious reaction occurs with a generic product, there is no means of determining whether it is an IgE-mediated allergy. Previous reports have shown that generic NMs contain significantly more unknown impurities than the original product, apart from hydrolysates.[22,25,26] Honda et al. indicated that products many contaminants are more likely to have side effects due to unidentified substances.[25] However, the components of these unknown substances have not yet been comprehensively investigated.

Immediately after the start of HD, adverse reactions may occur within a short time due to contact of the dialysis circuit and drugs with the blood. Our patient experienced life-threatening anaphylaxis immediately after NM administration on HD even though the allergy test results were negative. This is a rare but life-threatening complication of NM during HD. Therefore, it is important to pay attention to unpredictable complications and monitor patients closely immediately after the start of HD. To avoid adverse events in the next dialysis session, it may be helpful to change the anticoagulant and the dialysis circuit at the same time to ensure patient safety.

AUTHOR CONTRIBUTIONS

Nobuki Shioya involved in manuscript design and writing. Nozomu Inoue, Hiroki Sato, Motoko Iwahara, Tomohiro Sato, Yuki Tsukamoto, Yuki Naito, Kohji Hazama, and Yasuo Shichiohe treated and involved in manuscript revision.

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CONFLICT OF INTEREST

None.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICAL APPROVAL

Written informed consent was obtained from the patient's family.

CONSENT

Written informed consent was obtained from the patient's family to publish this report in accordance with the journal's patient consent policy.

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