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Usefulness of Plasma Exchange for Hypertriglyceridemia - Induced Severe Acute Pancreatitis: Report of Three Cases

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Abstract

Hypertriglyceridemia (HTG) is known to be a major cause of acute pancreatitis (AP). Since hyperlipidemia-induced AP may have a worse outcome, increased level of triglyceride (TG) should be immediately reduced to prevent deterioration of AP. We report three cases of HTG-induced severe acute pancreatitis (SAP) treated effectively using plasma exchange for reduction of increased TG level.

According to Japanese criteria for severity assessment of AP, three patients were diagnosed as having SAP by prognostic factors and CT grade. TG levels in the three patients were increased to 1381, 3125 and 10320 mg/dL, respectively. After plasma exchange once or twice, TG levels declined to almost normal levels. In all cases, AP-induced inflammatory response was attenuated and prognostic factors were decreased. Our three cases were successfully treated in a short period during ICU stay without progress of pancreatitis.

Since severe HTG, which means serum level of TG is more than 1000 mg/dL, is considered a risk for pancreatitis, it is important to reduce TG level immediately. Molecular weight of TG is 870-880 Da. However, continuous renal replacement therapy cannot remove TG because it is present in blood as a chylomicron or very low-density lipoprotein with a molecular weight of more than 50 kDa. It is thought that early interventions including plasma exchange for reduction of increased TG level might result in favorable outcome. We consider that rapid decline in increased TG levels of more than 1000 mg/dL by plasma exchange may improve pancreatitis without deterioration or recurrence.

Keywords: Severe acute pancreatitis; Hypertriglyceridemia; Plasma exchange

Introduction

There are various causes of severe acute pancreatitis (SAP) such as alcohol, gallstone disease, hyperlipidemia and several drugs. Hypertriglyceridemia (HTG) is known to be a major cause of acute pancreatitis (AP) next to alcohol and gallstone disease [1,2]. Hyperlipidemia-induced AP may have a worse outcome than AP from other causes [3]. Therefore, increased level of triglyceride (TG) should be immediately reduced to prevent deterioration of AP. We report three cases of HTG-induced SAP treated effectively using plasma exchange for reduction of increased TG level.

Case 1

A 41-year-old female with alcoholic liver dysfunction visited an outpatient clinic because of abrupt abdominal pain and bowel distension. The patient had HTG for 8 years but did not receive any medication. The patient drinks socially.

On admission to the clinic, the patient had slight malnutrition (height: 164 cm, weight: 55 kg, body mass index [BMI]: 20.4). Notable abnormal vital signs and physical findings were not observed, except for abdominal muscle defense sign and tetany in upper limbs. According to the Japanese criteria for severity assessment of acute pancreatitis [4], the patient was diagnosed as having SAP by the findings of blood analysis and CT imaging (prognostic factors: 4, CT grade: 3) (Figure 1). Then the patient was transferred to our ICU for further treatment.

Results of blood analysis (white blood cell count [WBC], 21900 /μL; C-reactive protein [CRP], 16.0 mg/dL) revealed severe inflammation response to AP (Table 1). There were AP-induced hypocalcemia (serum Ca of 5.7 mg/dL) and acute kidney injury (serum creatinine of 2.2 mg/dL) on admission to our ICU. Liver function disorder including asparate aminotransferase of 245 IU/L, alanine aminotransferase of 357 IU/L, lactate dehydrogenase of 687 IU/L, alkaline phosphatase of 409 IU/L, γ-glutamyl transpeptidase of 1021 IU/L was also observed; however, these data were considered to be influenced by not only AP but also alcoholic

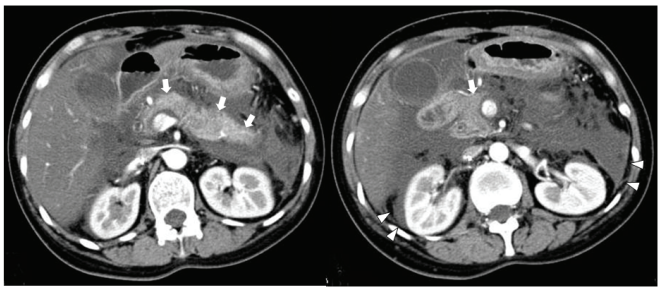

Figure 1: CT imaging of abdomen (Case 1)

Table 1: Laboratory data on admission to the ICU (Case 1)

WBC	21900/μL	**TP**	6.3 g/dL	**Na**	131 mEq/L
	(3900-9800)		(6.5-8.0)		(135-150)
Neutro	88%	**Alb**	3.3 g/dL	**K**	3.7 mEq/L
			(3.7-5.2)		(3.5-5.3)
Lymph	8.60%	**T-Bil**	3 mg/dL	**Cl**	89 mEq/L
			(0.2-1.2)		(95-108)
Mono	3.30%	**AST**	245 IU/L	**Ca**	5.7 mEq/L
			(11-39)		(8.4-10.4)
Eosino	0%	**ALT**	357 IU/L	**T-Chol**	238 mEq/L
			(5-40)		(120-219)
Baso	0.10%	**LD**	687 IU/L	**TG**	1381 mg/dL
			(119-229)		(40-149)
RBC	479 × 104/μL	**ALP**	409 IU/L	**BS**	224 mg/dL
	(430-570)		(110-370)		(65-95)
Hb	17.6 g/dL	**γ-GTP**	1021 IU/L	**Lac**	20 mg/dL
	(13.4-17.6)		(9-32)		(5-12)
Hct	48.90%	**CK**	325 IU/L		
	(39.6-52.0)		(71-220)	**[room air]**	
Plt	27.5 × 104/μL	**Amy**	395 IU/L	**pH**	7.38
	(12.7-35.6)		(37-120)		(7.35-7.45)
PT-INR	1.67	**BUN**	17 mg/dL	**PaCO2**	34 mmHg
	(0.85-1.15)		(6-20)		(32-48)
Fbg	293 mg/dL	**Cr**	2.2 mg/dL	**PaO2**	94 mmHg
	(200-400)		(0.6-1.0)		(83-108)
FDP	6 μg/mL	**CRP**	16 mg/dL	**BE**	-4.6 mmol/L
	(0.0-4.9)		(0.0-0.3)		(-2.3-2.7)
AT-III	24%			**$HCO3^-$**	19.7 mmol/L
	(80-130)				(21.2-27.0)

liver disease. The patient was treated with fluid resuscitation, enteral nutrition via a nasojejunal tube, selective digestive decontamination, continuous infusion of a protease inhibitor, empiric antibiotics, and continuous renal replacement therapy (CRRT). Also, plasma exchange was performed on the first ICU day and the second ICU day because serum TG level was increased to 1381 mg/dL.

After plasma exchange on two consecutive days, the increased TG level decreased to 43 mg/dL on the 3rd ICU day. As a result of aggressive treatment for AP, acute kidney injury was improved and the patient was weaned from CRRT on the 4th ICU day. On the 6th ICU day, AP-induced systemic inflammation was improved and prognostic factors of AP were decreased to 1. The patient was discharged from the ICU to the general ward for conventional treatment.

Case 2

A 38-year-old female who has untreated HTG for 23 years visited an outpatient clinic because of severe abdominal pain and back pain. Abdominal computed tomography showed a widespread low density area around the pancreas (Figure 2). According to blood analysis and CT findings, the patient was diagnosed as having SAP (prognostic factors: 6, CT grade: 2) and was admitted to our hospital on the same day. After admission to our hospital, SAP-associated clinical symptoms rapidly deteriorated, and the patient was transferred to our ICU for further treatment. The patient drinks on a social basis.

The patient was slightly obese (height: 163 cm, weight: 67 kg, BMI: 25.2). She was intubated and received mechanical ventilation because of acute respiratory failure. Treatment included fluid resuscitation, enteral feeding via a nasojejunal tube, selective digestive decontamination, administration of a protease inhibitor and antibiotics, and CRRT. Results of blood analysis (WBC, 21600 /μL; CRP 35.3 mg/dL) showed severe inflammatory response due to AP (Table 2). Also, pancreatitis caused elevation of lactate dehydrogenase (365 IU/L) and hypocalcemia (serum Ca of 6.7 mg/dL). Plasma exchange was performed on the first ICU day because serum TG level was increased to 3125 mg/dL.

After performing a single plasma exchange, TG level decreased to 270 mg/dL on the 3rd ICU day. Although oliguria persisted, CRRT was continued until the 6th ICU day. Prone ventilation was also performed to improve impaired oxygenation due to bilateral dorsal consolidation. On the 6th ICU day, AP-induced inflammatory response was attenuated and the patient was weaned from mechanical ventilation. Prognostic factors were decreased to 1 on the 8th ICU day. The patient was discharged from the ICU to the general ward on the 10th ICU day.

Case 3

A 39-year-old male who was being treated with oral medication for diabetes mellitus, dyslipidemia and hyperuricemia visited an outpatient clinic because of epigastric to lower abdominal pain. Results of blood analysis revealed elevations of serum TG and glucose. The patient was transferred to our emergency center due to reinforcement of abdominal symptoms. The patient drinks 400 milliliters of distilled spirits per day once a week.

On admission to the emergency center, serum TG and total cholesterol were increased to 10320 mg/dL and 1200 mg/dL, respectively. After several inspections, the patient was diagnosed as having mild acute pancreatitis and was treated by intravenous fluid replacement and antibiotics. However, he was transferred to the ICU because the severity score of AP fulfilled the criteria of severe AP (prognostic factors: 3, CT grade: 2) on the 2nd EC day (Figure 3).

The patient was obese (height: 176 cm, weight: 90 kg, BMI: 29.1). On admission to the ICU, CRP was increased to 45.4 mg/dL and arterial blood gas analysis showed severe metabolic acidosis (base excess: -18.3 mmol/L, pH: 7.28) (Table 3). Serum levels of TG and total cholesterol

Table 2: Laboratory data on admission to the ICU (Case 2)

WBC	21600/μL	**TP**	5.2 g/dL	**Na**	130 mEq/L
	(3900-9800)		(6.5-8.0)		(135-150)
Neutro	90.20%	**Alb**	2.7g/dL	**K**	3.5 mEq/L
			(3.7-5.2)		(3.5-5.3)
Lymph	4.90%	**T-Bil**	0.6 mg/dL	**Cl**	102 mEq/L
			(0.2-1.2)		(95-108)
Mono	4.60%	**AST**	16 IU/L	**Ca**	6.7 mEq/L
			(11-39)		(8.4-10.4)
Eosino	0.20%	**ALT**	10 IU/L	**TG**	3125 mg/dL
			(5-40)		(40-149)
Baso	0.10%	**LD**	365 IU/L	**BS**	177 mg/dL
			(119-229)		(65-95)
RBC	412 × 104/μL	**ALP**	167 IU/L	**Lac**	11 mg/dL
	(430-570)		(110-370)		(5-12)
Hb	12.2g/dL	**CK**	84 IU/L		
	(13.4-17.6)		(71-220)	**[O2 mask 3L/min]**	
Hct	36.70%	**Amy**	238 IU/L	**pH**	7.28
	(39.6-52.0)		(37-120)		(7.35-7.45)
Plt	21.9 × 104/μL	**Lipase**	266 IU/L	**PaCO2**	45mmHg
	(12.7-35.6)		(9-48)		(32-48)
PT-INR	1.23	**BUN**	7 mg/dL	**PaO2**	88 mmHg
	(0.85-1.15)		(6-20)		(83-108)
Fbg	636 mg/dL	**Cr**	0.3 mg/dL	**BE**	-4.8 mmol/L
	(200-400)		(0.6-1.0)		(-2.3-2.7)
FDP	15 μg/mL	**CRP**	35.3 mg/dL	**$HCO3^-$**	20.4 mmol/L
	(0.0-4.9)		(0.0-0.3)		(21.2-27.0)
AT-III	54%				
	(80-130)				

Table 3: Laboratory data on admission to the ICU (Case 3)

WBC	6700/μL	**TP**	5.8 g/dL	**Na**	127 mEq/L
	(3900-9800)		(6.5-8.0)		(135-150)
Neutro	81.7%	**Alb**	2.6 g/dL	**K**	3.6 mEq/L
			(3.7-5.2)		(3.5-5.3)
Lymph	10.9%	**T-Bil**	0.4 mg/dL	**Cl**	97 mEq/L
			(0.2-1.2)		(95-108)
Mono	5.1%	**AST**	14 IU/L	**Ca**	7.5 mEq/L
			(11-39)		(8.4-10.4)
Eosino	2.2%	**ALT**	5 IU/L	**T-Chol**	647 mg/dL
			(5-40)		(120-219)
Baso	0.1%	**LD**	315 IU/L	**TG**	1758 mg/dL
			(119-229)		(40-149)
RBC	397 10^4/μL	**ALP**	130 IU/L	**BS**	218 mg/dL
	(430-570)		(110-370)		(65-95)
Hb	11.7 g/dL	**CK**	67 IU/L	**Lac**	10 mg/dL
	(13.4-17.6)		(71-220)		(5-12)
Hct	34%	**Amy**	125 IU/L		
	(39.6-52.0)		(37-120)	[room air]	
Plt	15 × 10^4/μL	**BUN**	5 mg/dL	**pH**	7.28
	(12.7-35.6)		(6-20)		(7.35-7.45)
PT-INR	1.28	**Cr**	0.5 mg/dL	**PaCO2**	17 mmHg
	(0.85-1.15)		(0.6-1.0)		(32-48)
Fbg	735 mg/dL	**CRP**	45.4 mg/dL	**PaO2**	93 mmHg
	(200-400)		(0.0-0.3)		(83-108)
FDP	13 μg/mL			**BE**	-18.3 mmol/L
	(0.0-4.9)				(-3.2-1.8)
				$HCO3^-$	11.6 mmol/L
					(22.2-28.3)

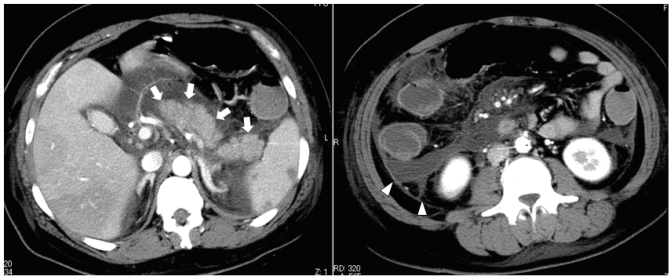

Figure 2: CT imaging of abdomen (Case 2)

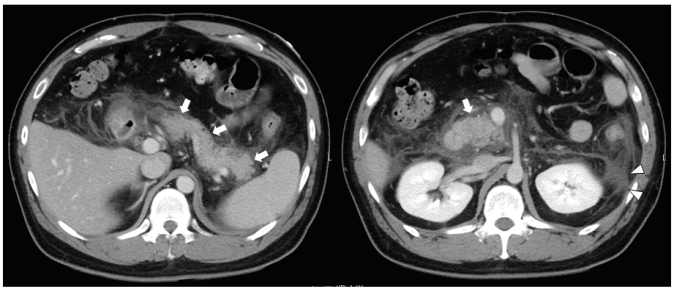

Figure 3: CT imaging of abdomen (Case 3)

were decreased to 1758 mg/dL and 647 mg/dL, respectively, but were still high. Therefore, plasma exchange was performed on the 2nd ICU day and the 3rd ICU day. CRRT was also started on the 2nd ICU day.

After plasma exchange on two consecutive days, the increased TG and total cholesterol levels declined to 160 mg/dL and 287 mg/dL, respectively, on the 4th ICU day. CRRT was continued until the 4th ICU day. Since the patient's condition improved and prognostic factors were decreased to zero, the patients was discharged from the ICU on the 6th ICU day and medical treatment was continued in the general ward.

Discussion

SAP is a systemic inflammatory disease mediated by various inflammatory mediators such as cytokines released by local inflammation of the pancreas, and systemic inflammation can develop to multiple organ dysfunction syndrome despite recent advances in intensive care management. Therefore, regulation of mediators plays an important role in the treatment of SAP. Japanese guidelines for AP recommend CRRT as an optional treatment for the regulation of AP-induced storms of inflammatory mediators. However, there is evidence of efficacy of CRRT for SAP because of the diversity of CRRT methods such as duration, replacement dose and type of hemofilter.

It has been reported that HTG-induced AP accounts for only 1.3–3.8% of all cases of AP [2]. Anderson and co-workers showed that HTG may account for up to 10% of all cases of AP [5]. Maximal TG level was showed to be a risk factor for the development of pancreatitis [6]. TG level of more than 1000 mg/dL has been suggested to be a risk level for AP [2,7]. It has also been reported that 85% of HTG patients with AP had a maximal TG level of more than 3000 mg/dL [8]. However, there was no correlation between TG level and severity of pancreatitis [6].

Patients with HTG-induced AP have clinical features of high BMI and young age at onset compared with those of patients with AP caused by other factors [9]. All of our three patients were around forty years of age, and two of them had BMI of more than 25. According to the results of a cohort study on HTG-induced pancreatitis [8], the severity of pancreatitis is greater than that of pancreatitis caused by alcohol or gallstones. Another study by Deng et al. [3] also showed that patients with pancreatitis and HTG had a higher rate of complications and a higher rate of mortality than those for patients with pancreatitis who do not have HTG. Unlike these reports, however, our three cases were successfully treated in a short period during ICU stay without progress of severe pancreatitis. It is thought that early interventions including plasma exchange for reduction of increased TG level might result in favorable outcome.

The pathogenesis of AP caused by HTG is still unclear. Havel et al. [10] reported the most acceptable theory for mechanisms underlying the onset of HTG-induced pancreatitis: pancreatic lipase that is released into the vascular bed of the pancreas hydrolyzes excess TG and the hydrolyzed TG induces release of a large amount of free fatty acids. A large amount of released free fatty acids will aggregate into micellar structures and attack platelets, vascular endothelium and acinar cells, resulting in pancreatic ischemia and injury. There is another theory that plasma hyperviscosity is caused an increased level of chylomicrons, which may be a result of ischemia and acidosis in pancreatic capillaries [11]. On the other hand, it has been pointed out that pancreatitis can potentially induce HTG [12]. Uchida et al. [13] reported that tumor necrosis factor-α, one of the inflammatory cytokines that are usually released in AP, has a suppressive effect on lipoprotein lipase activity in brown adipocytes.

In patients with HTG-induced SAP, therefore, it is important to reduce the serum level of TG immediately. The molecular weight of TG is 870-880 Da, which is removable by CRRT. However, CRRT cannot remove TG, because TG is present in blood as chylomicrons or very low-density lipoproteins that are generated to substances with a molecular weight of more than 50 kDa. Serum level of TG is known to be reduced by fasting and conservative treatment in a few days [14,15], and appropriate therapy can therefore reduce an increased TG level in a few days. However, the serum level of TG should be reduced immediately in patients with HTG-

induced AP because HTG may cause and worsen AP in a rapid sequence. Consequently, only plasma exchange, which can achieve the removal of high molecular-weight substances easily and quickly, is considered to be an effective and useful treatment for SAP with HTG [16,17]. In our cases, rapid decline in increased TG levels by plasma exchange seemed to improve the pancreatitis without deterioration or recurrence. However, the indication for plasma exchange therapy depending on the level of TG in patients with AP remains unclear. Since severe HTG (TG of >1000 mg/dL) is considered a risk for pancreatitis [18], we carry out plasma exchange for HTG-induced SAP if TG level is more than 1000 mg/dL.

On the other hand, it is necessary to consider that plasma exchange, which needs a large quantity of fresh frozen plasma, may cause unknown viral infection, complications such as anaphylactic reaction or transfusion-related acute lung injury, and hypocalcemia due to citric acid included in the fresh frozen plasma. Furthermore, plasma exchange is a rather expensive treatment and is not available in all institutes [6]. Therefore, we should select plasma exchange therapy when the merits of this treatment would overwhelm its demerits in patients with AP. Moreover, the fact that plasma exchange reduces mortality and morbidity in patients with HTG-induced AP is not sufficient to justify its use. More clinical data and a randomized control study are necessary to prove the validity of plasma exchange for treatment of TG-induced AP.

Conclusion

We reported three cases of HTG-induced SAP treated with plasma exchange. Plasma exchange was performed on the first ICU day in two cases and after deterioration of pancreatitis in the other case. Since all cases showed favorable recovery, plasma exchange for rapid decrease in TG level seems to play an important role in preventing deterioration and recurrence of HTG-induced AP.

Authors' Contributions

TH - Treated the three patients as ICU doctor and drafted the manuscript.

MY - Treated the three patients as ICU doctor, participated in the design of the study and helped to draft the manuscript.

TK, HM and YS - Treated the three patients as ICU doctor.

OM and MM - Treated the three patients as internal physician and helped to draft the manuscript.

KY and YM - Helped to draft the manuscript.

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All authors read and approved the final manuscript.

Competing Interest

The authors declare that they have no competing interests. The authors have no affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the article.

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