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LDL Apheresis in Cholesterol Crystal Embolization Patients: 6 Case Reports

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Cholesterol crystal embolism (CCE) occurs when an atherosclerotic plaque is disrupted and cholesterol crystals within the plaque or portions of the plaque embolize distally. Although various therapies have been applied for its treatment, an effective method has yet to be developed. We herein presented six patients with CCE who underwent low-density lipoprotein apheresis (LDL-A), with satisfactory outcomes being achieved in four. Our patients were diagnosed with CCE and underwent LDL-A between April 2008 to April 2014. A retrospective examination was performed on the presence or absence of improvements in cutaneous lesions and renal function; improvements were observed in four patients. Dialysis was initiated for the two patients who did not achieve improvements. Serum creatinine levels before the onset of CCE were significantly higher in the two patients receiving hemodialysis than in the four patients with improved cutaneous lesions and renal function. The results of this study suggest that LDL-A may be an effective treatment for CCE, and its effectiveness may be increased if patients have satisfactory renal function before the onset of CCE.

Key words: cholesterol crystal embolism, LDL apheresis, outcome

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INTRODUCTION

Cholesterol Crystal Embolism (CCE) was first reported in 1945 by Flory *et al.* [1], and is a condition in which cholesterol crystals on large vessel walls detach, resulting in systemic small vessel occlusions. In many cases, CCE is triggered by mechanical and chemical injuries, including instrumentation of the vasculature (such as angiography), cardiovascular surgery, and anticoagulant therapy. Symptoms include renal impairment, hematuria, proteinuria, cutaneous manifestations, and eosinophilia. The five characteristic symptoms of CCE have been reported as lower extremity pain, livedo reticularis, palpable peripheral arteries, progressive renal failure, and a history of instrumentation of the vasculature. Although a treatment method has not yet been established, various treatments have been reported including the discontinuation of anticoagulants and use of steroid therapy, ARB, statins, low-density lipoprotein apheresis (LDL-A), and plasmapheresis.

Only a few studies have examined the effects of LDL-A on CCE. However, LDL-A has been shown to affect peripheral arterial disease (PAD). The effects of LDL-A may be interpreted mechanistically as follows; improvements in blood and plasma viscosity [2], anti-inflammatory effects [3-5], and vasodilatory effects [6, 7]. LDL-A is considered to have similar effects in CCE patients, leading to its effectiveness in ameliorating the disease. However, an effective method has not yet been developed. We herein presented six patients with CCE who underwent LDL-A and achieved satisfactory outcomes in four patients.

SUBJECTS AND METHODS

Our subjects were patients who were diagnosed with CCE and underwent LDL-A between April 2008 and April 2014 at Shimane University Hospital. A retrospective examination was performed on the presence or absence of improvements in cutaneous lesions and renal function after LDL-A. In all subjects, LDL-A was performed using an adsorption system with a Liposorber LA-15 column. LDL-A involved 3000 ml of plasma processed per session and 50 mg/hr of nafamostat mesilate used as an anticoagulant. The number of apheresis sessions varied between subjects and ranged from 3 to 10.

The serum creatinine (S-Cr) level before the onset of CCE was the average S-Cr level from three months before the likely triggering event of CCE [coronary angiography (CAG) or surgery] until to its diagnosis. This average was established as the S-Cr level before the onset of CCE. S-Cr at the onset of CCE was established as S-Cr at the diagnosis of CCE, while S-Cr at the commencement of LDL-A was established as S-Cr at the first LDL-A session. S-Cr after LDL-A was the average S-Cr level from two months after LDL-A. Improvements in skin lesions were defined as the disappearance of Blue toe syndrome, while deteriorations were defined as the absence of changes and aggravated symptoms. Improvements in renal function were defined as lower S-Cr after LDL-A than at the onset.

This study was performed in accordance with the Declaration of Helsinki and was approved by the Institutional Ethics Committee of Shimane University Faculty of Medicine (Study Number 1694).

RESULTS

Five male patients and 1 female patient, with an average age of 73.3 years (Table 1), participated in this study. The underlying diseases were hypertension (HT) in four cases, diabetes mellitus (DM) in three cases, chronic kidney disease (CKD) in three cases, abdominal aortic aneurysm (AAA) in two cases, familial hypercholesterolemia in one case (Case 4), and dilated cardiomyopathy in one case. The cause of CCE was CAG in three cases, anticoagulant therapy in one case, surgery for AAA in one case, and AAA + disseminated intravascular coagulation (DIC) in one case. The average number of LDL-A sessions for CCE was 6.7 (3-10). Although LDL-A led to improvements in four cases, it was ineffective in two cases, which resulted in the initiation of hemodialysis (HD).

The average age was 72.8 years in the improved group and 74.5 years in the HD group (Table 2). There were three men and one woman in the improved group and two men in the HD group. The underlying diseases were three cases of HT and two cases of DM in the improved group. S-Cr before the onset of CCE was 2.00 mg/dL in the improved group and 4.67 mg/dL in the HD group. All patients in the improved group took prednisolone as oral pharmacotherapy, while three patients took statin. Only an angiotensin II receptor blocker (ARB) was used in the HD group. Since it was difficult to obtain good treatment results in the HD group, the number of LDL-A sessions was significantly higher in the HD group than in the improved group.

The clinical course of each patient is described below.

Case 1: The patient was a 62-year-old woman who had been receiving ongoing outpatient care for HT, DM, and CKD (S-Cr: 3.29 mg/dL). She was admitted for heart failure and underwent CAG. Renal dysfunction (S-Cr 4.47 mg/dL) and eosinophilia were observed from the 19th day after CAG, and Blue toe syndrome was observed on the 24th day. The diagnosis of CCE was made by skin biopsy, and the patient received 20 mg/day of prednisolone and underwent a total of three LDL-A sessions. Blue toe syndrome and renal function subsequently improved. The patient was subsequently discharged.

Case 2: The patient was a 72-year-old man who had been receiving outpatient care for CKD (S-Cr: 1.63mg/dL). An internal carotid artery plaque and basilar artery stenosis were detected. The patient began receiving oral clopidogrel, but developed a rash on the lower limbs after two months. Since a drug rash was suspected, clopidogrel was discontinued and steroids were initiated. However, the skin lesions did not improve and became slightly exacerbated. Peripheral blood flow was satisfactory, and skin biopsy did not show any findings of CCE. The

Table 1. Baseline characteristics of our patients

	Age (yr)	Sex	Pre S-Cr (mg/dL)	Onset S-Cr (mg/dL)	S-Cr at LDL-A start (mg/dL)	S-Cr after LDL-A (mg/dL)	Eo (%)	Combination Therapy	Number of LDL-A	Cause	Outcome	
											Renal function	Skin lesion
①	66	F	3.29	4.47	4.05	3.73	13.6	PSL 20 mg/day	3	CAG	Improve	Improve
②	72	M	1.63	3.99	4.29	3.2	2.8	PSL 20 mg/day	7	Anticoagulation	Improve	Improve
③	82	M	1.47	2.22	2.01	1.75	13.2	PSL 20 mg/day+Statin	4	AAA+DIC	Improve	Improve
④	71	M	5.51	10.57	8.01	3.05	10.1	no	10	CAG	HD	Worse
⑤	78	M	3.82	7.35	11.65	4.64	0	no	10	AAA Surgery	HD	Worse
⑥	71	M	1.59	2.68	2.65	2.37	17.1	PSL 10 mg/day+Statin	6	CAG	Improve	improve
Average	73		2.89	5.21	5.44	3.12	9.5		6.7			

Eo: Eosinophil, PSL: Prednisolone, CAG: Coronary Angiography
AAA: Abdominal Aortic Aneurysm, HD: Hemodialysis, DIC: Disseminated Intravascular Coagulation
S-Cr:Serum Creatinine

Table 2. Results

	Improve (N=4) Case 1,2,3,6	HD (N=2) Case 4, 5
Age (yr)	72.8	74.5
Sex	M 3, F 1	M 2, F 0
Hypertension (n)	3	1
Type Ⅱ DM (n)	2	1
Pre S-Cr (mg/dL)	2.00	4.67
Onset S-Cr (mg/dL)	3.34	8.96
Creatinine at LDL-A start (mg/dL)	3.25	9.83
Creatinine after LDL-A (mg/dL)	2.76	3.85
Duration of the event and LDL-A start (day)	71	25
Duration of the diagnosis and LDL-A start (day)	15	11
Doubling of S-Cr or initiation of HD at the onset (n)	1	1
Doubling of S-Cr or initiation of HD at 1st LDL-A (n)	1	2
Prednisolone (mg)	13	0
Statin (n)	3	0
ACEi/ ARB (n)	3	1
Number of LDL-A (n)	5	10

HD: Hemodialysis, DM: Diabetes mellitus
S-Cr: Serum Creatinine

diagnosis of CCE was made based on the clinical course. Since renal function declined (S-Cr: 3.99 mg/dL), the patient underwent a total of seven LDL-A sessions. The skin rash gradually improved and renal function also became better.

Case 3: The patient was an 82-year-old man who had been receiving outpatient care for HT and hyperlipidemia. His S-Cr level was 1.47 mg/dL before the onset of CCE. The patient developed exercise-induced chest tightness and was admitted for a thorough examination of the coronary arteries (The patient did not underwent CAG.). Plain abdominal CT scans showed AAA. The International Society on Thrombosis and Hemostasis score was 5 points, and DIC was diagnosed. The cause of DIC appeared to be AAA. Blue toe syndrome was detected on the plantar surfaces, and renal dysfunction (S-Cr: 2.2mg/dL) was also observed. CCE was diagnosed by skin biopsy. The patient received 4 mg/day of pitavastatin and 20 mg/day of prednisolone and underwent a total of four LDL-A sessions. Cutaneous lesions and renal function improved, and the patient was transferred to the Surgery department for the treatment of AAA.

Case 4: The patient was a 71-year-old man with a S-Cr level of 5.51 mg/dL before the onset of CCE. His symptoms resembled those of an acute upper respiratory tract infection and he presented to a nearby hospital. He was admitted to another hospital due to heart failure, renal dysfunction, and pleural effusion. The patient was transferred to our hospital for a thorough examination of heart failure and underwent CAG. HD was initiated because the patient was in end-stage renal failure at the time of his transfer to our hospital. Erythema of the bilateral soles developed one month after CAG, and CCE was diagnosed. We did not administer a steroid because he had ischemic heart disease, brain infarction, and a gangrenous foot. Although ten LDL-A sessions were performed, no improvements were observed in the cutaneous lesions. The patient had multiple decubitus due to prolonged bedrest and his nutritional status had gradually deteriorated. The patient did not want to undergo aggressive treatments and was transferred to another hospital.

Case 5: The patient was a 78-year-old man who had been receiving outpatient care for CKD (S-Cr: 3.82 mg/dL). He was admitted to the Cardiovascular Surgery department to undergo surgery for AAA, and Y-graft replacement was performed. The patient developed necrosis of the bilateral soles after surgery. Intraoperative findings showed multiple intraaortic plaques as well as eosinophilia. CCE was diagnosed based on the clinical course. Renal dysfunction (S-Cr: 7.35 mg/dL) was observed. We did not administer steroids because he had CKD G5 due to severe DM. The patient began receiving HD and underwent 10 LDL-A sessions; however, his cutaneous lesions and renal function did not improve. HD was continued, and the patient was transferred to another hospital for rehabilitation.

Case 6: The patient was a 71-year-old man with a S-Cr level of 1.59 mg/dL before the onset of CCE. He was admitted for chronic heart failure, underwent CAG, and was discharged. Renal dysfunction and eosinophilia were observed two months after CAG. The patient was readmitted for diuretic adjustments three months after the examination. Eosinophilia and Blue toe syndrome of the lower limbs were subsequently observed. CCE was diagnosed by skin biopsy. The patient received 10 mg /day of prednisolone and underwent six LDL-A sessions. His cutaneous lesions and renal function improved. The patient was subsequently discharged.

DISCUSSION

Table 3 summarizes studies on LDL-A for the treatment of CCE. Variations were observed in the number of LDL-A sessions and use of combination therapy. However, all reported cases achieved improvements in renal function and/or skin lesions. These findings suggested that LDL-A may be effective for CCE. However, ineffective cases may not have been reported. Since these were case reports, large scale prospective studies are needed in the future in order to evaluate the clinical effectiveness of LDL-A for CCE.

In the present case series, two out of six patients showed no improvement in cutaneous lesions or renal function. Case 4 had malnutrition and decubitus, while Case 5 had CKD stage 5 since before the onset of CCE. Therefore, it was unlikely that CCE only caused renal dysfunction. The S-Cr level

Table 3. Summary of reported cases of LDL-A for CCE

Age (yr)	Sex	Combination Therapy	Onset S-Cr (mg/ dL)	Number of LDL-A	Outcomes	
					Renal function	Skin legion
68[8]	M	PG analog	N.D.	10	Improve	Improve
68[8]	M	Statin, PG analog, HD	N.D.	10	Unchanged	Improve
66[9]	M	PSL 20 mg/day, HD	8.1	5	Improve	Improve
68[10]	M	PSL 20 mg/day, HD, ARB	5.69	10	Improve	Improve
76[11]	M	Limaprost alfadex	2	20	Improve	Improve
74[12]	M	PSL 20 mg/day, Statin	2.1	10	Improve	Improve

PSL: Prednisolone, PG: Prostaglandin, HD: Hemodialysis, ARB: angiotensin II receptor blocker
N.D.: No Data, S-Cr: Serum Creatinine

before the onset of CCE was significantly lower in the improved group than in the HD group. Thus, LDL-A may be more effective in patients with lower S-Cr before the onset of CCE. Satisfactory renal function before the onset of CCE may predict the good recovery of renal function by LDL-A. No significant differences were observed in S-Cr at the onset of CCE, S-Cr at the commencement of LDL-A, doubling of S-Cr, or use of HD between the two groups. The effects of LDL-A may not depend on the extent of renal dysfunction induced by CCE. LDL-A may be effective regardless of the extent of renal dysfunction due to CCE. There were only six patients in the present case series, and this small number was insufficient for statistical processing. This was also a retrospective study, and variations were noted in patient backgrounds and treatment contents. Therefore, a definitive conclusion cannot be reached regarding the effectiveness of LDL-A. Further studies are needed with more cases in order to identify CCE patients for whom LDL-A will be effective.

CONCLUSION

The results of the present study suggest that LDL-A may be an effective treatment for CCE. The effects of LDL-A may not depend on the extent of renal dysfunction by CCE. LDL-A for CCE may be more effective if renal function prior to the onset of CCE is good. Further studies are needed with more cases in order to identify CCE patients for whom LDL-A will be effective.

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