Renal Replacement Therapy

CASE REPORT

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An autopsy case of a patient on maintenance hemodialysis with continuous idiopathic cholesterol crystal embolism for 7 years

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Abstract

Background CCE is a systemic disease with poor prognosis with no established treatment. Approximately 23–32% of CCE cases progress to end-stage renal failure, and the 1-year mortality rate of CCE with organ failure is 60–90%. The dialysis method for the patients with CCE is still controversial.

Case report The patient is 73 years old male who was diagnosed with idiopathic CCE. He had survived 7 years though he had been on maintenance HD. We used nafamostat for HD every time. He took prednisolone and statin. He died due to rupture of AAA and we autopsied him. CCs developed in five organs, including the right lung CCE was assumed to be continuously present since the diagnosis.

Discussion and conclusion CCE was continuous until death, and CCs in the right lung were possibly due to HD. HD through AV shunt could worsen CCE, and HD should be recognized as the aggravating factor. The use of nafamostat while undergoing HD as well as use of steroids and statins until death may have prevented fatal events and contributed to the patient's long survival.

Keywords Cholesterol crystal embolism, Idiopathic cholesterol crystal embolism, Autopsy, Maintenance hemodialysis, Nafamostat

Background

CCE (Cholesterol crystal embolism) is a systemic disease with poor prognosis caused by formation of cholesterol crystal emboli in multiple organs. Approximately 23–32% of CCE cases progress to end-stage renal failure, and the 1-year mortality rate of CCE with organ failure is 60–90% [1]. In addition, at a mean follow-up of 5 years, end-stage renal disease and death have been reported to occur in 24% and 38% CCE cases, respectively [2]. There is no established treatment for CCE [3]. Idiopathic CCE occurs without endovascular manipulation, accounts for approximately 20% CCE cases, and is rare compared with iatrogenic CCE [2].

Case presentation

X-7 years 73 years old male was admitted to our hospital because of progressive renal failure. Two months before admission, he was diagnosed with atherosclerotic brain infarction and treated by oral antiplatelet therapy (100-mg aspirin daily). Since then, his creatinine level had worsened gradually for 2 months. Blue toe was noticed on his big left toe, and skin biopsy was taken. He was diagnosed with CCE as skin biopsy showed CC (Fig. 1). We stopped the administration of aspirin and prescribed 20-mg (0.33 mg/kg daily) oral prednisolone, but his renal failure had progressed. Maintenance hemodialysis (HD)

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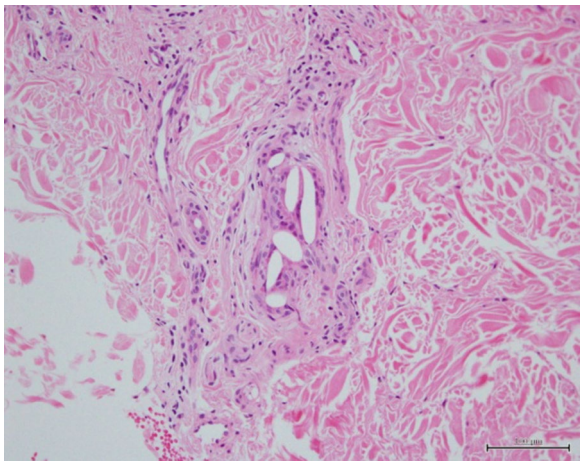

Fig. 1 Cholesterol clefts in skin at the diagnosis 7 years before admission. CCs are surrounded with leukocytes without fibrosis, and these are the acute findings

was initiated one month after the diagnosis. Prednisolone was reduced to 10 mg (0.17 mg/kg) daily and we used nafamostat for HD every time. LDL-C (Low-density lipoprotein cholesterol) had been well controlled with atorvastatin. He was discharged after initiation of HD through artery and vein shunt (AV) shunt. He had been stable for 7 years since the initiation of HD. His condition was good enough, and he could come to our hospital all by himself to undergo maintenance HD. He received ESA (erythropoiesis stimulating agent) occasionally depends on Hemoglobin while HD. D-dimer had been continuously below 6 μg/mL, which did not suggest chronic disseminated intravascular coagulation. Eosinophil count had been under 500.

X-1 year He became forgetful and Alzheimer's disease was suspected.

X-16 days He had become agitated and irritated gradually and was admitted to our hospital for evaluation.

The patient was in an agitated state and had lost weight. He took 10-mg prednisolone (0.25 mg/kg) daily. Results of blood panel are shown in Table 1. CT(Computed tomography) and magnetic resonance imaging of the brain revealed no new cerebrovascular abnormality. Chest and abdominal CT showed aortic aneurysm. The maximum diameter of the aneurysm was 53.6 mm and 48.6 mm in the chest and abdominal aorta, respectively, which is not indicative of surgical treatment in elderly people. We considered Alzheimer's disease as the most likely condition and initiated palliative care. On the seventh day, the patient developed blue toe syndrome on his right toe; however, we did not perform an additional skin biopsy as CCE was already diagnosed. On the 19th day, the patient demonstrated delayed responsiveness

Table 1 Results of blood panel on admission

WBC	8700/μL
Neutrophils	7720/μL
Eosinophils	230/μL
Basophil	100/μL
Lymphocytes	670/μL
Monocyte	70/μL
%Neutro	88.8%
%Eosino	2.6%
%Baso	0.1%
%Mono	0.8%
%Lympho	7.7%
RBC	3,54,000/μL
Hb	12 g/dL
Hct	35.4%
MCV	92.2 fL
MCH	31.4 pg
MCHC	34.2%
PLT	2,67,000/μL
TP	5.8 g/dL
Alb	3.4 mg/dL
BUN	59.5 mg/dL
Cr	5.21 mg/dL
AST	12 U/L
ALT	6 U/L
LDH	197 IU/L
ALP	193 IU/L
γGTP	11 IU/L
T-Bil	0.4 mg/dL
CPK	23 IU/L
Na	130 mEq/L
Cl	96 mEq/L
K	4.3 mEq/L
IP	5.6 mg/dL
Corrected Ca	8.5 mg/dL
BNP	1044.3 pg/mL
Ferritin	126 ng/mL
LDL	108 mg/dL

at 10 min after a stimulus of routine care by the nurse. Although we attempted resuscitation, he died. Results of the blood test conducted during resuscitation did not reveal the cause of death. D-dimer at the death was 20.3 μg/mL. Systemic CT after death revealed rupture of an aortic aneurysm, resulting in bleeding to the intraperitoneal area. An autopsy was performed.

His medical history included CCE, hypertension, atherothromboric cerebral infarction (7 years prior), gastric ulcer (5 years prior), compression infarction and severe drug eruption (3 years prior). He took oral prednisolone (10 mg), furosemide (120 mg), carvedilol (10 mg),

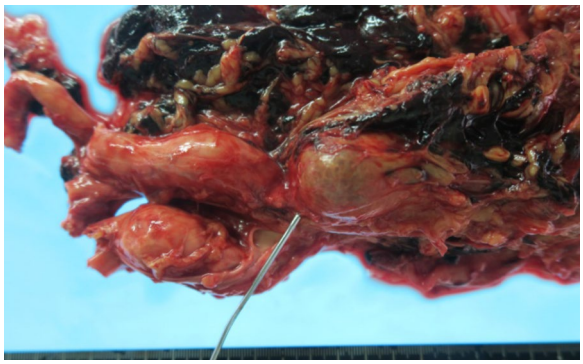

Fig. 2 Rupture of aortic aneurism

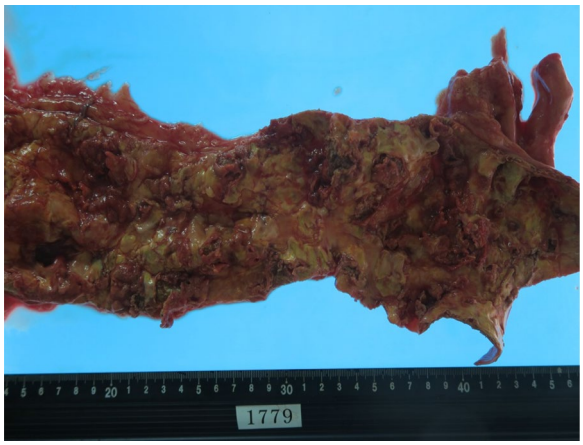

Fig. 3 Atherosclerosis of the aortic intima

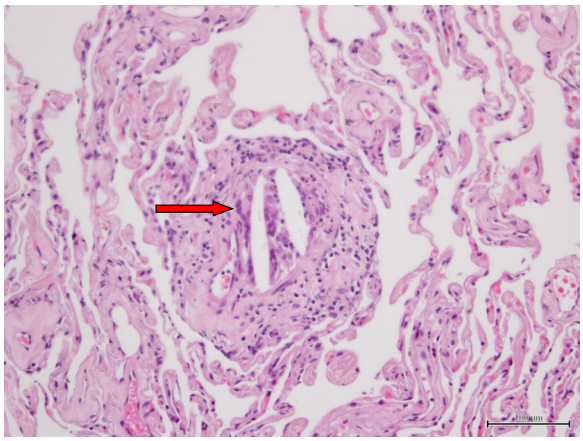

Fig. 4 CC in the right lung. Leucocytes infiltrate the region around CCs without fibrosis. Multinucleated histiocytes (red arrow) are observed around CCs

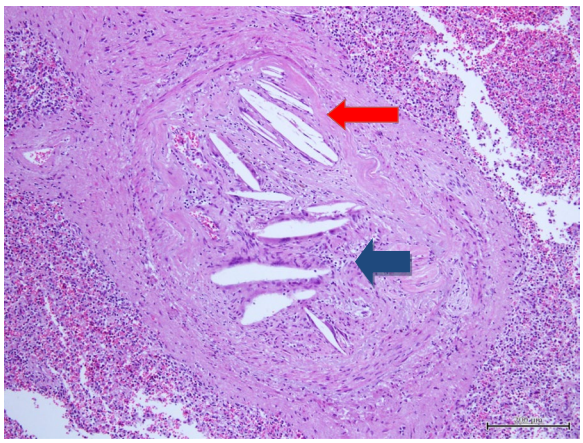

Fig. 5 CC in the spleen. Leukocytes (blue arrow) infiltrate the region around CCs, but fibrosis (red arrow) around CCs is also observed

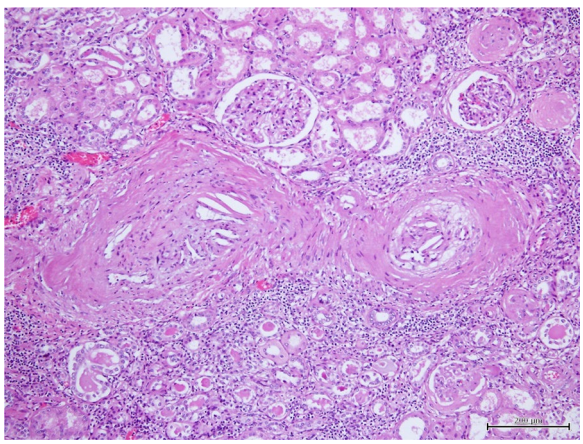

Fig. 6 CC in the kidney surrounded with fibrosis and leukocytes

sulfamethoxazole (800 mg), trimethoprim (160 mg), lansoprazole (30 mg), atorvastatin calcium hydrate (5 mg), febuxostat (5 mg), risperidone (1 mg), and Yokukansan (7.5 mg), which is a Chinese medicine, daily. He had been smoking 20 cigarettes per day until 7 years ago and he is occasional alcohol drinker.

Autopsy result

Autopsy was performed 9 h and 48 min after death. Findings revealed abdominal aortic aneurisms (AAA) from the inferior mesenteric artery level to the level of both common iliac arteries. Rupture of the aneurism on the left side of the lower mesenteric artery was considered to be the direct cause of death (Fig. 2). The aorta was found to have extensive atherosclerosis, from the thoracic aorta to the abdominal aorta, from which CCE seemed to develop (Fig. 3). CCs were occluded in multiple organs, including the right lung (Fig. 4), spleen (Fig. 5), kidneys (Fig. 6), adrenal gland (Fig. 7), and skin (Fig. 8). In the lungs, CCs were found in the right upper lobe, and not in the left lung. Atherosclerosis was not

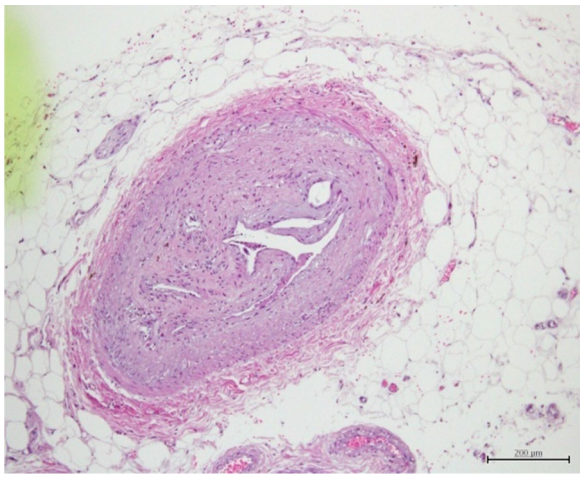

Fig. 7 CC in the adrenal glands surrounded with fibrosis. These seem to be old findings

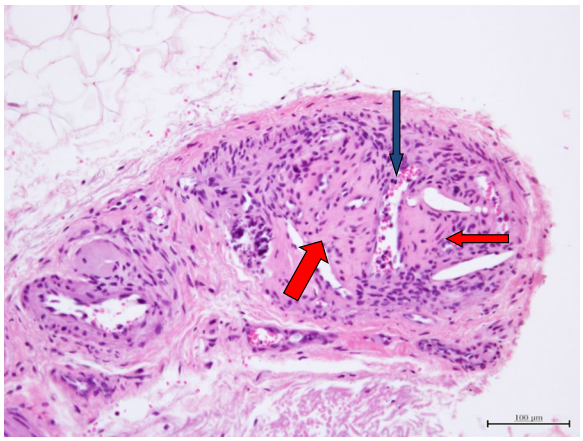

Fig. 8 CC in the skin. Leukocytes infiltrate the region around CC. Neovascular (blue arrow) and granulation tissue (red arrow) are seen

noted in the pulmonary arteries. We could not identify bronchial arteries owing to massive atherosclerosis in the aorta. Multinucleated histiocytes around CCs were observed in the lung (Fig. 4). CCs in the spleen (Fig. 5) and the kidneys (Fig. 6) were surrounded by leukocytes accompanied by fibrosis. These acute to subacute findings suggested that CCE had occurred even after the diagnosis. On the other hand, CCs in the adrenal gland (Fig. 7) were surrounded by fibrosis without leukocytes. Neovascular and granulation tissue are observed in the skin (Fig. 8). These findings suggested that considerable time had passed since CCs developed. The onset of CCE seems to be diverse and this suggests that CC has continued since diagnosis. Signs of a previous myocardial infarction were also found.

Discussion

Reportedly, end-stage renal disease and death occurred in 24% and 38% cases of CCE, respectively, at a mean follow-up of 5 years [2]. Irrespective of that, there exists no established treatment for CCE. Our patient survived for 7 years after the diagnosis of CCE even though he had end-stage renal failure and was undergoing HD.

CCE is divided into two types. Iatrogenic CCE that occurs following endovascular manipulation and anticoagulation therapy accounts for approximately 80% of CCE cases. Idiopathic CCE that occurs without the use of such maneuvers accounts for approximately 20% of cases [1]. Our patient underwent only antiplatelet therapy for atherosclerotic brain infarction; therefore, we diagnosed him with idiopathic CCE. We assumed this case as very rare not only because of idiopathic CCE but also because the patient survived long period of 7 years, owing to which we had performed an autopsy.

CCE develops following peripheral artery occlusion caused by needle-shaped cholesterol crystals that are detached from ruptured atheromatous plaques or fibrin microthrombi [4]. Fries et al. reported that of the 51 autopsies performed for CCE cases, 29 were found to have CCs in just one organ. The organs most affected were the kidneys (71%), spleen (37%), and lower gastrointestinal tract (22%). The lungs were affected to a lower extent (5.9%, the detail was not reported). Only one of the 51 cases had CCs in 5 organs, and all others had CCs in 2–4 organs [4]. In this study, CCs were found in five organs. CCE seems to have developed for 7 years until death, as acute to subacute CCs were found in the spleen and kidney. CCs can potentially travel via the systemic circulation through the bronchial arteries. Another way CCs can occur in the lungs could be via the pulmonary artery [5]. However, CCs in the lungs are distinctly uncommon in the absence of arteriovenous fistula [6]. Our literature search revealed only six cases with CCs in the lungs that were detected via autopsy or biopsy (Table2). Of these, four cases had AV shunt for HD [7–10]. In one case, CCE occurred after surgical repair of an abdominal aortic aneurysm tear with an aortocaval fistula [11]. In one case, the presence of AV shunt was not clearly manifested, although the patient was undergoing HD. The possibility of an AV shunt in any other organ like the liver or brain was discussed in a previous report [5]. In our study, CCs were found in the right upper lung lobe only, and there was no atherosclerosis in the pulmonary arteries. CCs in the right lung were assumed to have originated from aortic atherosclerosis through the AV shunt. Blood access other than AV shunt such as subcutaneously fixed superficial artery and peritoneal dialysis (PD) could be the first

Table 2 6 cases CCs in the lungs were detected

Reference No	Author and year	AVshunt	HD	Autopsy
[7]	Amari Y (2010)	Present	Done	Done
[8]	Nakakoji Y (2011)	AV shunt for HD	Done	Done
[9]	Kono Y (2006)	AV shunt for HD	Done	Done
[10]	Kojima M (2012)	AV shunt for HD	Not done	Done
[11]	Weigent CE (1978)	An aortocaval fistula after surgery	Not done	Done
[5]	Sabatine MS (1997)	Not manifested	Done	Not done An open-lung biopsy

choice for such patients requiring dialysis to avoid fatal CC occlusion into lungs via the AV shunt [7, 12].

Reportedly, CCE exacerbates with the use of an anticoagulation drug. Anticoagulation therapy itself could be the cause of iatrogenic CCE. Although only case reports have been reported regarding the dialysis method; moreover, it is still unclear as to which anticoagulation drugs are the best for HD. Few studies have reported on worsening of CCE following HD using heparin [7, 8, 13, 14]. Sugawara also reported the case of an outpatient undergoing HD who was stable for 5 years with the use of LMWH (low-molecular weight heparin) [14]. HD should be recognized as a factor that can exacerbate CCE, for which should be considered. PD, which avoids the use of an anticoagulation drug, could thus be the first choice for the patients requiring dialysis not to aggravate CCE [7]. In the present study, we used nafamostat for our patient, which appeared beneficial as we did not observe any fatal event, embolic shower, or bleeding.

There is no established treatment for CCE. Currently, there are no large trials evaluating therapies for treating patients with CCE. Regarding the mechanism of CCE, embolization of CCs causes ischemic injury, and the subsequent inflammatory reaction aggravates and perpetuates the injury [15]. Not only the CCs but also the fibrin clots forming around CCs obstruct the peripheral arteries, causing tissue infarction and organ failure [5]. Endothelial injury, complement activation, oxidative stress, activation of the renin–angiotensin–aldosterone system, leukocyte aggregation, and release of leukocyte enzymes are all considered responsible for end-organ injury. CCs cause inflammatory reactions around the arterioles resembling a foreign-body giant cell reaction. The complement pathway is also an important aspect of CCE [16]. Thus, anti-inflammatory agents such as steroids may be effective in CCE [17, 18]. However, recent reports have shown an effective improvement (Table3) [19–23]. The effectiveness, effective amount of steroid, and effective duration of prescription are still unknown. Similar to the patient in our study, a previous study reported that the patient survived 5 years while receiving 10 mg prednisolone daily. In addition, cessation of prednisolone aggravated skin symptoms and eosinophilia, for which prednisolone was initiated and continued [14]. In the present study, we had prescribed 20 mg prednisolone for a month and continued 10 mg prednisolone daily until patient death, and it seemed to benefit the patient as CCE did not aggravate until death even though CCE had occurred after the diagnosis. Recently colchicine or cyclophosphamide has been suggested to be effective. CCs activate the IL1β pathway via the NLRP3 inflammasome molecule and induce TNF and MIP2 secretion. This NLRP3/IL1 pathway in the pathogenesis of CCE was recently discovered, and

Table 3 Steroid dosage that was effective in the case reports

Reference No	Author and year	Number of patients	Steroid dosage and duration
[19]	Nakayama M (2006)	7	15–20 mg/day for 2–4 weeks, tapered to 5 mg/day over 2–4 weeks, followed by 5 mg/day maintenance dose
[20]	Boero R (2000)	7	5 cases: 0.3 mg/kg BW/day for 3 months 1 case: oral therapy was preceded by daily IV pulses of methylprednisolone, 125 mg for 5 days 1 cases: oral therapy was preceded by daily intravenous pulses of 250 mg for 3 days
[21]	Koga J (2005)	1	30 mg (0.4 mg/kg)
[22]	S J Mann (2001)	1	50 mg
[23]	F Fabbian (1999)	1	50 mg/day after 250 mg methylprednisolone IV, decreased 25 mg/day

the efficacy of IL1 antagonists (canakinumab) has been investigated [15].

Aortic atherosclerotic plaque is an important source of CCE. A study reported that among 519 patients with thoracic aortic atherosclerotic plaques, 1% had CCE at > 3 years [24]. When idiopathic CCE is diagnosed, the presence of aortic plaque should be investigated as it could be the source of CCE. Older age, male sex, smoking, heart failure, peripheral vascular disease, cerebrovascular disease, renal insufficiency, DM(Diabetes Mellitus), hypertension, and aortic aneurism and dissection have been significantly associated with a higher frequency of CCE [4, 25], and these are also the well-known factors of atherosclerotic plaque. We believe that controlling these factors is considerably important to prevent and manage both atherosclerosis and CCE. We could not find the direct relation between CCE, its prognosis and DM but DM is definitely a strong risk factor of CCE. Takahashi et al. [26] report that 40% of CCE patient had DM. Anemia could be caused by CCE [15]. However, Hb level of maintenance HD patient is well controlled by ESA like this patient. Statins may provide primary beneficial effects against CCE by lowering LDL-C levels, stabilizing atherosclerotic plaques, and mediating pleiotropic anti-inflammatory effects [15]. Scolari reported that baseline treatment of LDL-C reduced the risk of end-stage renal disease and improved 1-year cumulative survival [2]. Tunick reported that statin reduces the ratio of embolic event from thoracic aortic plaque with an odds ratio of 0.3 [24]. LDL-C apheresis is also a choice for treatment [27]. This patient had extensive atherosclerosis from the thoracic aorta to abdominal aorta, from which CCE seemed to develop. LDL-C was well controlled with statins, and the patient discontinued smoking after diagnosis.

In summary, we report an autopsy case of a patient undergoing maintenance HD who developed idiopathic CCE and survived for 7 years. CCE was supposed to be continuous since the diagnosis and develop into five organs over 7 years. CCs in the right lung might have developed via HD through the AV shunt. The use of nafamostat while undergoing HD could prevent a fatal event. Prednisolone 10 mg daily might help in controlling inflammation caused by CCE. Aortic atherosclerotic plaque is an important source of CCE, and statins could help stabilize atherosclerotic plaques. Nafamostat, steroids, and statins could prevent fatal events and contribute to long survival.

Abbreviations

CCE	Cholesterol crystal embolism
HD	Hemodialysis
AAA	Aortic abdominal aneurism
AV shunt	Artery and vein shunt
LDL-C	Low-density lipoprotein cholesterol
CT	Computed tomography
LMWH	Low-molecular weight heparin
DM	Diabetes mellitus
ESA	Erythropoiesis stimulating agent

Acknowledgements
Not applicable

Author contributions
Not applicable.

Funding
Not applicable.

Availability of data and materials
All data generated or analyzed during this study are included in this published article.

Declarations

Ethics approval and consent to participate
Not applicable.

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

Competing interests
The authors declare that they have no competing interests.

Received: 22 February 2022 Accepted: 20 April 2023
Published online: 03 May 2023

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