

[ CASE REPORT ]

## An Autopsy Case of Acute Pancreatitis Caused by Cholesterol Crystal Embolization

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### Abstract:

Cholesterol crystal embolization (CCE) shows a poor prognosis and it can cause ischemic organ damage due to a cholesterol embolism from atherosclerotic lesions in large blood vessels. Such an embolism mainly affects the kidneys and skin, although cases involving digestive organs have also been reported. We encountered an autopsy case of CCE with damage mainly to the digestive organs, including the pancreas. The patient had non-specific abdominal symptoms or image findings. Symptomatic therapy failed to save him. CCE can involve the digestive organs, and so must be differentiated from abdominal pathologies. Moreover, conventional treatments may be ineffective, and new treatments might thus be necessary.

**Key words:** cholesterol crystal embolization, pancreatitis, digestive organ, LDL apheresis

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### Introduction

Cholesterol crystal embolization (CCE) causes organ ischemic damage due to the occurrence of cholesterol embolisms from atherosclerotic lesions in large blood vessels (1). Such embolisms mainly affect the kidneys and skin, but some cases involving the organs of the digestive system have also been reported. However, diagnosing CCE of digestive organs is difficult in clinical practice because of the low index of suspicion and the difficulty of obtaining appropriate samples by biopsy (2), and few reports have shown the detailed clinical course. In addition, established treatments are lacking, and the prognosis is poor (1). Recently, new treatments have been reported for CCE of the kidneys and skin (3-7). We herein present a case of pancreatitis caused by CCE, in which the symptoms were mainly related to the digestive organs and standard therapy failed to avert a rapid deterioration thus resulting in death.

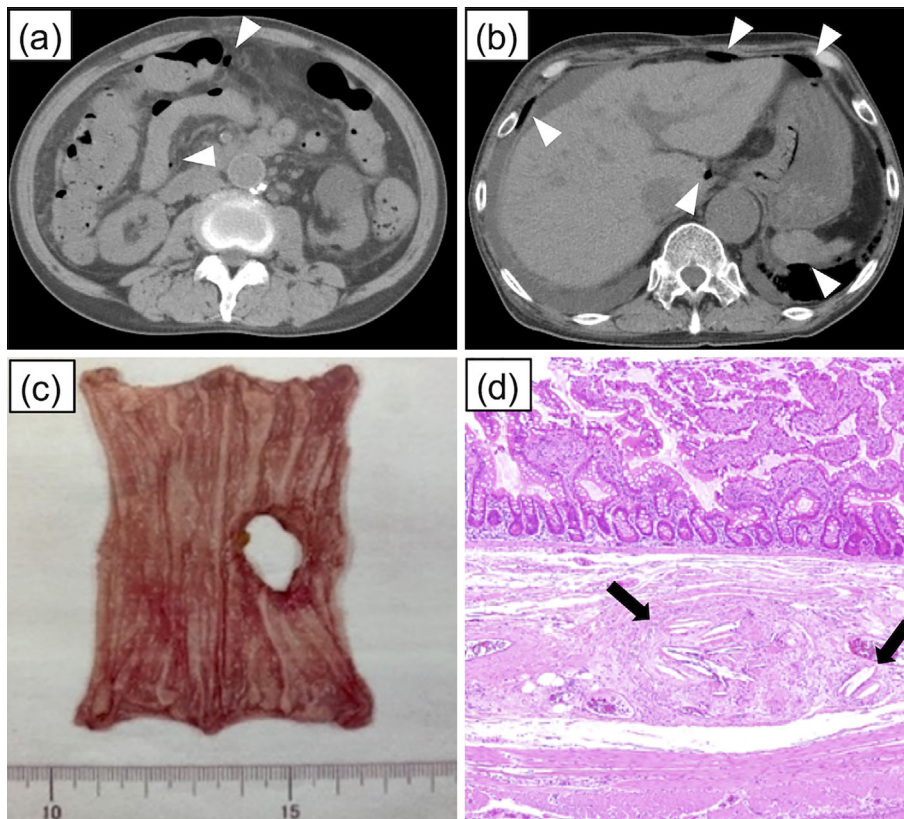
### Case Report

A 59-year-old man was admitted to another hospital with an acute exacerbation of chronic obstructive pulmonary disease. He was a smoker with a history of Burger's disease and surgery for vascular replacement and artery bypass (31 years old), acute myocardial infarction (45 years old), chronic heart failure and cerebral infarction (51 years old), chronic kidney disease (progressed from 3 years earlier), hypertension and unexplained thrombocytopenia. During the course of treatment, small intestinal perforations occurred twice and surgical treatment was performed. The first time, the patient experienced abdominal pain accompanied by high levels of CRP (5.72 mg/dL) and WBC (15,200/ $\mu$ L) and CT showed free air in the abdominal cavity (Fig. 1a). An emergency operation revealed a small intestinal perforation and partial resection of the perforated part was performed. The second time, 50 days after the first time, he had a similar process and CT showed free air in the abdominal cavity

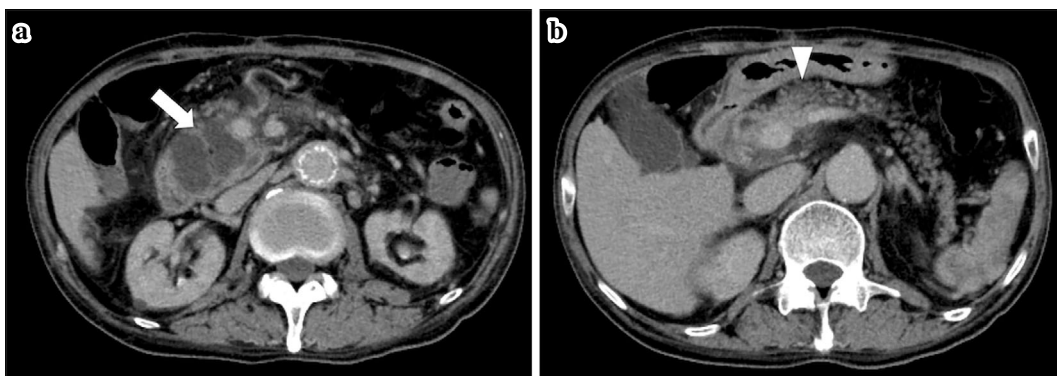
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**Figure 1.** Images of abdominal CT during perforation of the small intestine, and macroscopic and histological findings of a resected specimen of the first time perforated small intestine. (a) The first time, CT showed free air in the abdominal cavity (arrowheads). (b) The second time, CT showed free air in the abdominal cavity (arrowheads). (c) Perforation, 18 mm, in small intestinal mucosa (arrow). (d) Cholesterol crystals are identified within the lumen of small arteries (arrows), indicating the presence of cholesterol crystal embolisms ( $\times 40$ ).

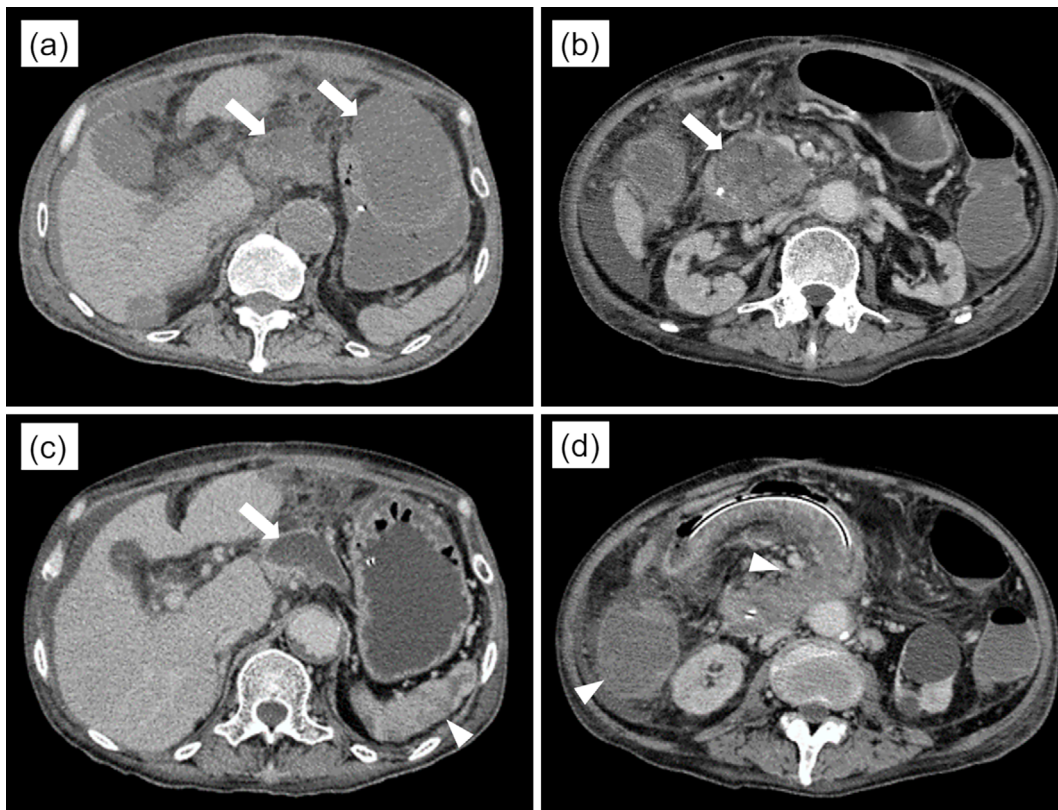


**Figure 2.** Images of abdominal contrast-enhanced CT during pancreatitis at a previous hospital. (a) Contrast-enhanced CT shows a cyst in the pancreatic head (arrow). (b) Contrast-enhanced CT shows no enlargement of the pancreas (arrowhead).

again (Fig. 1b). An emergency operation revealed the recurrence of small intestinal perforation and ended with a simple closure. Histologically, ischemic changes to the intestinal mucosa and blood vessels filled with cholesterol emboli were observed around these perforations (Fig. 1c, d). One month after surgery, he again experienced strong abdominal pain and blood testing showed high levels of serum CRP (20.5 mg/dL) and pancreatic amylase (479 U/L). Computed

tomography (CT) showed some pancreatic cysts, but no enlargement of the pancreas (Fig. 2). Acute pancreatitis was diagnosed and treatment with fasting, massive infusion, and pain control were initiated. He obtained some relief from the symptoms, but experienced repeated recurrences of acute pancreatitis and was therefore transferred to our hospital.

On admission, abdominal pain was reduced, and blood tests showed slightly elevated serum CRP (1.49 mg/dL) and



**Figure 3.** Images of abdominal CT during the course in our hospital. (a) CT shows cysts in the pancreatic body and anterior of the stomach (arrows) from the main pancreatic duct. (b) Contrast-enhanced CT shows a cyst in the pancreatic head (arrow). (c) Contrast-enhanced CT shows a cyst in the pancreatic body (arrow) and poor contrast areas in the spleen (arrowhead). (d) Contrast-enhanced CT shows a poor contrast in the jejunum and ascending colon (arrowheads).

pancreatic amylase (131 U/L) levels. Enteral nutrition was carefully initiated via a jejunal tube. However, marked abdominal pain recurred and blood tests showed elevated serum CRP (9.5 mg/dL) and pancreatic amylase (787 U/L). CT showed multiple ectopic metachronous cystic lesions in the pancreas, without any noticeable swelling of the pancreas or inflammation of surrounding tissues (Fig. 3a-c). Ischemic findings for the jejunum, colon, and spleen were also apparent (Fig. 3c, d).

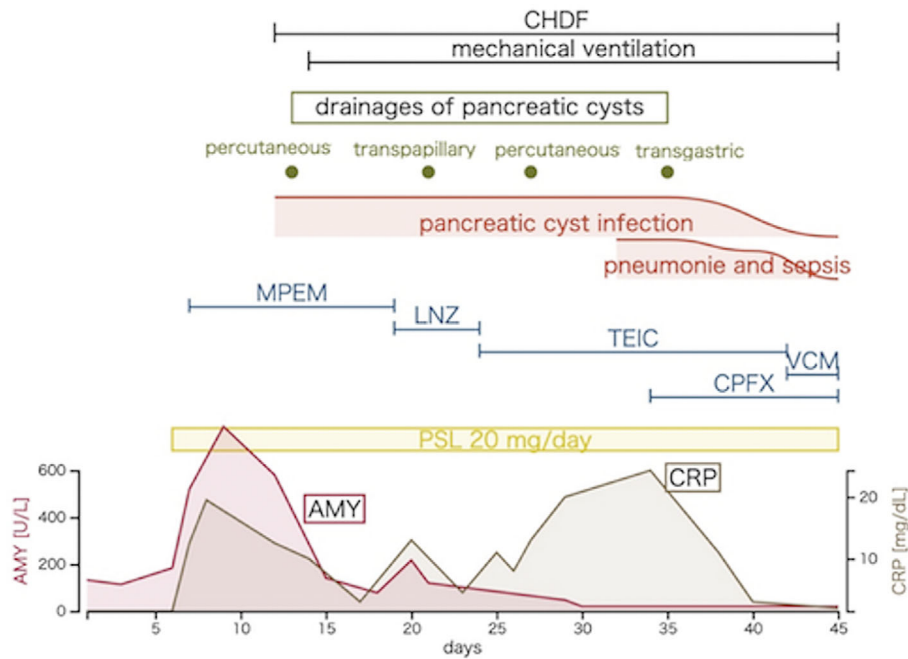
Hydroxymethylglutaryl-CoA (HMG-CoA) reductase inhibitor, prostaglandin (PG) E1, and steroids were used in addition to fasting and infusion as treatment for acute pancreatitis, because we suspected of cholesterol embolisms from a history of perforation of small intestine, ischemic findings of multiple organs, and atypical pancreatitis course. However, no improvements were seen in the abdominal pain, serum CRP, or cyst formation. Day 10 in our hospital, continuous hemodiafiltration was started because of acute kidney failure and with the aim of adsorbing inflammatory cytokines. The abdominal pain proved difficult to control even with fentanyl. The patient's respiratory condition worsened due to pleural effusion, so mechanical ventilation was also started.

The multiple pancreatic cysts were suspected to represent infectious foci causing abdominal pain, so percutaneous, transpapillary, and transgastric drainages of the pancreatic

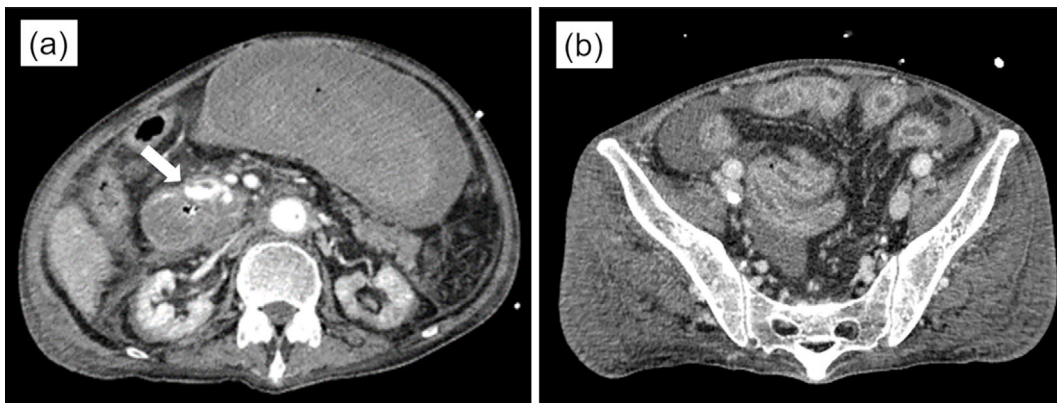
cysts were performed. The fluid collected by drainage had a markedly high level of amylase (25,408 U/L), confirming that it was pancreatic juice, and *Enterococcus faecium* was cultured from the fluid. In addition, pneumonia and subsequent sepsis caused by *Pseudomonas aeruginosa* developed, so antibiotic treatment was performed as appropriate. After treatment of the sepsis, the inflammation was finally subsided to some degree, and the course appeared to stabilize (Fig. 4).

However, Day 47, sudden hematemesis and bloody stool were observed. Contrast-enhanced CT showed the rupture of a pseudoaneurysm of the gastroduodenal artery secondary to pancreatitis and bleeding into pancreatic head cyst (Fig. 5a). We performed massive blood transfusion and stopped the bleeding with interventional radiology (IVR). However, severe diarrhea with some blood then occurred, and the patient's level of consciousness began to decline. CT showed prominent thickening of the intestinal walls (Fig. 5b), and extensive cerebral infarction. A stool culture was negative and clostridium difficile antigen and toxin were also negative. We thereafter stopped active treatment, and the patient finally died on Day 69 (Fig. 6).

Autopsy was performed with the consent of the family. The results showed severe atherosclerotic changes in the aorta (Fig. 7a, b) and cholesterol crystals in the pancreas,



**Figure 4.** Clinical course of this case from date of transfer to Day 45. CHDF: continuous hemodiafiltration, MPEM: meropenem, LNZ: linezolid, TEIC: teicoplanin, CPMX: ciprofloxacin, VCM: vancomycin, PSL: prednisolone, AMY: amylase, CRP: C-reactive protein



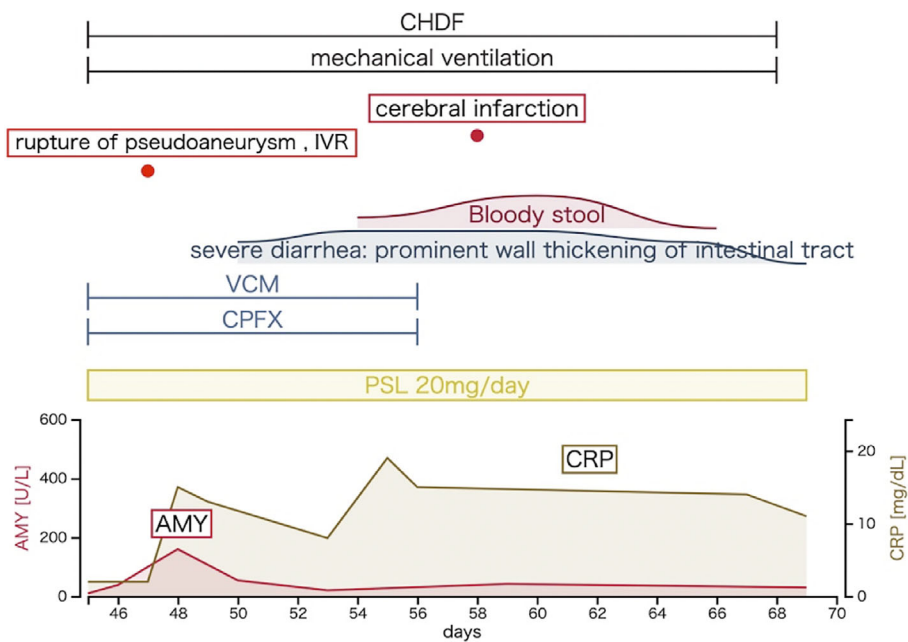
**Figure 5.** Images of abdominal CT during the course in our hospital. (a) Day 47, contrast-enhanced CT showed extravasation from gastroduodenal artery (arrow) and a full stomach with high absorption. (b) Day 54, contrast-enhanced CT shows significant wall thickening in the small and large intestines.

gastrointestinal organs, spleen, kidneys, liver, gallbladder, prostate, cerebrum, and skin. These crystals were considered to have contributed to infarction and ischemia in each organ (Fig. 7c-f). The pancreas showed fat necrosis, infiltration of inflammatory cells such as neutrophils, and pseudocysts with no lining epithelium. The cause of death was determined to be multi-organ failure due to ischemic inflammation of multiple organs caused by CCE and septic shock.

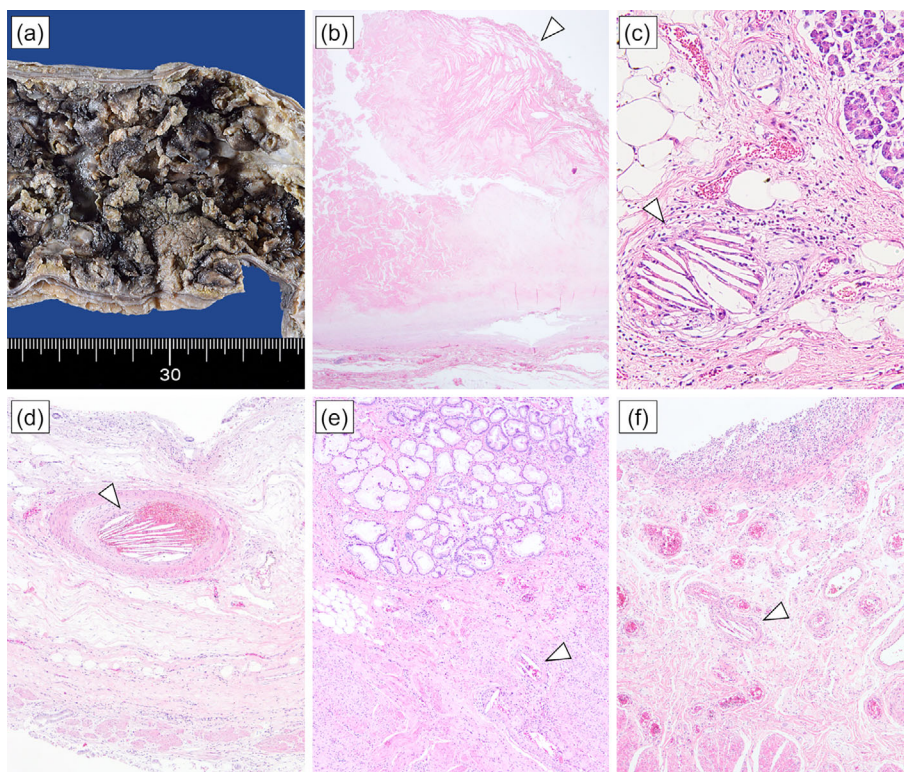
## Discussion

CCE is a systemic disease caused by cholesterol crystals or fibrin microthrombi exfoliated from atherosclerotic le-

sions in large blood vessels obstructing peripheral blood vessels throughout the body, and it shows a poor prognosis (1). Atherosclerosis is a risk factor, and CCE reportedly develops as a result of vascular manipulation or antithrombotic treatment, but 20% of cases are idiopathic (2, 8). Representative target organs are the kidneys and skin, accounting for around 50% of all CCE cases. Cases of CCE involving the digestive system are also sometimes reported, as the third most common site. According to a recent review, about 20% of CCE patients have at least one gastrointestinal organ disorder. Pancreatic damage is reported in about 10%, but this finding is considered to be underestimated because of the difficulties of making a differential diagnosis and per-



**Figure 6.** Clinical course of this case from Day 45 to the date of death. CHDF: continuous hemodiafiltration, IVR: interventional radiology, VCM: vancomycin, CPFX: ciprofloxacin, PSL: prednisolone, AMY: amylase, CRP: C-reactive protein



**Figure 7.** Macroscopic and histological findings of pathological autopsy specimens. Severe atherosclerosis (arrowhead) of the aorta on (a) macroscopic view and (b) histological examination ( $\times 12.5$ ). Cholesterol crystals (arrowheads) are seen in the (c) pancreas ( $\times 100$ ), (d) gallbladder ( $\times 100$ ), (e) duodenum ( $\times 100$ ), and (f) ileum ( $\times 40$ ).

forming tissue examinations (2). The symptoms take many forms, such as abdominal pain, diarrhea, bloody stool, and gastrointestinal perforation in the digestive tract. In the pan-

creas, symptoms can cover a wide spectrum, from nonspecific abdominal pain that may be misdiagnosed as functional dyspepsia to severe necrotizing pancreatitis, depending on

the parenchymal volume that is impaired (2, 9, 10).

In the present case of CCE, the affected areas were diverse, including the digestive tract, pancreas, spleen, gall bladder, liver, skin, eyes, kidneys, and brain. Pancreatitis was most noticeable, and the clinical findings were very unusual, showing multiple cysts that developed in various places and at intervals rather than the course of parenchymal swelling and spreading inflammation seen with typical pancreatitis. Autopsy showed no lining of glandular tissue inside the cysts. Histologically, the cause of pancreatitis and multiple pancreatic cysts were thought to be microscopic cholesterol crystals. These would have embolized the nutritional vessels of the pancreas, thus causing damage to the pancreatic parenchyma and pancreatic ducts in a small area, in turn causing ruptures of the pancreatic ducts and cyst formation. In addition, with regard to marked abdominal pain, abdominal angina seemed to be a stronger contributor than pancreatitis because of few changes in the pancreatic parenchyma and poor pain relief after cyst drainages.

Regarding the pancreatic pseudoaneurysm rupture, a hemorrhaging due to a rupture into the pancreatic head cyst first occurred, followed by leakage through the pancreatic duct to the duodenal lumen, which thus caused a slight increase of amylase from increased intraductal pressure. In addition, the gastrointestinal symptoms after IVR are considered to be ischemic changes due to CCE exacerbation. IVR might have scattered a large amount of cholesterol embolisms, thus affecting it more extensively than before. As a result, it worsened the overall condition, but there was no choice other than IVR to save the patient's life during bleeding. If pancreatic pseudoaneurysms have been diagnosed before bleeding, the choice of prophylactic IVR for CCE patients would be very difficult. The risk of their spontaneous rupture is high and the mortality rate of such ruptures is also high, so if diagnosed, it may be inevitable to treat (11). However, it would be better to first perform plaque stabilization treatment as described below.

In this case, we suspected CCE as the cause of pancreatitis, but were unsure. The policy was to wait for symptoms to subside with symptomatic treatment, such as pain management, respiratory circulation management, and infection control, rather than provide direct treatment for CCE, but we could not save the patient. Considering that small intestine perforation occurred due to CCE, and that CCE easily spreads throughout the body with diverse symptoms, a diagnosis of CCE should have been reached.

No treatment methods specifically for CCE have been established, and symptomatic treatment is the mainstay around the world. The pathogenesis of CCE has been suggested to involve not only plaque rupture and mechanical occlusion of microvessels, but also the following three stages of inflammatory response: 1) acute inflammation; 2) foreign body reaction and intravascular thrombus formation; and 3) endothelial proliferation and fibrosis. During the acute inflammatory phase, the walls of the affected arterioles and small arteries are infiltrated by polymorphonuclear leukocytes and

eosinophils. Within the next 24 to 48 hours, mononuclear cells appear; they become giant cells, and they phagocytize cholesterol crystals. Around the same time, there is intraluminal thrombus formation. In the final stage, there is endothelial proliferation and intimal fibrosis. The net result is narrowing or even obliteration of the arterial lumen, thus leading to tissue ischemia (12). As an approach to this condition, HMG-CoA reductase inhibitors and steroids have been used to stabilize plaques and suppress inflammation, but their effects are limited (13). Recently, low-density lipoprotein (LDL) apheresis has occasionally been reported to be a more potent treatment (3-5). LDL apheresis reportedly exerts not only plaque-stabilizing effects by lowering the lipid levels (14), but also anti-inflammatory effects by removing inflammatory substances, and improvement of vascular function and blood flow by increasing nitric oxide, PG, and vascular endothelial growth factor, and so on (3-6). A new drug, evolocumab, an anti-proprotein convertase subtilisin/kexin type 9 (PCSK9) antibody, may also have beneficial effects on renal involvement in patients with CCE (7). Almost all of the reports on CCE have involved the kidneys and skin (3-5, 7), but the underlying pathology should be the same even for gastrointestinal organs. We therefore think these new treatments are worth investigating for CCE in the digestive field in the near future.

We herein reported an autopsy case of CCE that mainly resulted in damage to the digestive organs. CCE of gastrointestinal organs is not uncommon, but is difficult to diagnose clinically. Patients showing an abnormal abdominal clinical course who have a history of vascular disease or severe atherosclerosis should always have CCE included in the differential diagnosis, even in the absence of trigger factors. In addition, CCE has a poor prognosis and it is often difficult to save using conventional treatments as was observed in the present case. Evidence for new treatments such as LDL apheresis and evolocumab remains insufficient, but these options may be worth trying. Further accumulation of cases is therefore desired.

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

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