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【 CASE REPORT 】

# Cholesterol Crystal Embolism Induced by Direct Factor Xa Inhibitor: A First Case Report

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**Abstract:**
An 80-year-old man presented at our hospital with renal failure. He had been treated with edoxaban, an oral direct factor Xa inhibitor, for deep vein thrombosis for 10 months prior to admission. Although the pulses in his bilateral pedal arteries were palpable, cyanosis was present in the bilateral toes. Laboratory data indicated azotemia and eosinophilia. A skin biopsy confirmed a diagnosis of cholesterol crystal embolism (CCE). Because no invasive vascular procedure was performed, we assumed that CCE was related to edoxaban. To the best of our knowledge, this is the first case report suggesting CCE induced by an Xa inhibitor.

**Key words:** acute kidney injury, cholesterol crystal embolism, direct oral anticoagulants, edoxaban, renal failure, Xa inhibitors

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## Introduction

Cholesterol crystal embolism (CCE) is a systemic disease resulting from the occlusion of the arteries by cholesterol crystals released from atheromatous plaques of the aorta (1). Catheter or surgical manipulation of the aorta is a major cause of CCE, but it can occur spontaneously (2-4), as well as after thrombolysis or anticoagulants (1). Although warfarin is the most common causative anticoagulant, there are no case reports suggesting that any factor Xa inhibitor can cause CCE. There are two case reports in which Xa inhibitors were substituted for warfarin and achieved a complete resolution of CCE (5, 6). It is unclear why Xa inhibitors may be a useful treatment for CCE, and not a cause. In this case report, we describe the first case of CCE with renal failure induced by edoxaban, one of the Xa inhibitors.

## Case Report

An 80-year-old man was admitted to our hospital with renal failure and general fatigue. He had a history of hypertension and ischemic stroke with a moderate hemiparetic gait. He also had a history of septic arthritis and deep vein thrombosis (DVT) during his stay in the orthopedic ward at our hospital 11 months prior to this admission. Edoxaban, one of the direct factor Xa inhibitors, was started for the treatment of DVT about 10 months prior to this admission.

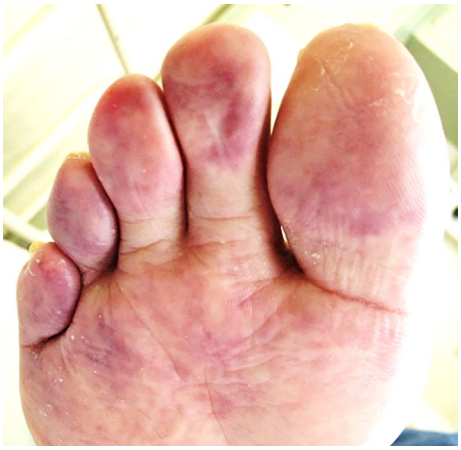

**Figure 1.** **Blue-colored toes of the right foot.**

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**Table. Laboratory Data on Admission.**

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Hematological values | | | Blood chemical values | | | Immunological study | | |
| White blood cell count | 15,880 | /μL | Total protein | 6.5 | g/dL | C-reactive protein | 17.55 | mg/dL |
| Neutrophil | 73.0 | % | Albumin | 2.9 | g/dL | Complement 3 | 101.1 | mg/dL |
| Lymphocyte | 8.0 | % | Total bilirubin | 0.2 | mg/dL | Complement 4 | 31.0 | mg/dL |
| Monocyte | 3.0 | % | Aspartate aminotransferase | 40 | U/L | Serum complement titer | 50.1 | U/mL |
| Eosinophil | 16.0 | % | Alanine aminotransferase | 19 | U/L | Immunoglobulin G | 2,478.2 | mg/dL |
| Red blood cell count | $280\times10^4$ | /μL | Lactate dehydrogenase | 241 | U/L | Immunoglobulin A | 415.6 | mg/dL |
| Hemoglobin | 7.7 | g/dL | Creatine kinase | 48 | U/L | Immunoglobulin M | 72.4 | mg/dL |
| Hematocrit | 22.8 | % | Blood urea nitrogen | 41.4 | mg/dL | MPO-ANCA | <0.5 | U/mL |
| MCV | 83.5 | fL | Creatinine | 2.34 | mg/dL | PR3-ANCA | <0.5 | U/mL |
| MCHC | 32.0 | g/dL | Uric acid | 6.6 | mg/dL | Coagulation test | | |
| Platelet count | $26.4\times10^4$ | /μL | Sodium | 135 | mEq/L | PT-INR | 1.15 | |
| Venous blood gas | | | Potassium | 5.3 | mEq/L | APTT | 33.1 | s |
| pH | 7.314 | | Chloride | 110 | mEq/L | Urinary chemistry | | |
| $pCO_2$ | 29.0 | mmHg | Transferrin saturation | 43 | % | Urinary sodium | 45 | mEq/L |
| $HCO_3$ | 14.3 | mmol/L | Ferritin | 75 | ng/mL | Urinary potassium | 25.7 | mEq/L |
| Urinalysis | | | Calcium | 8.8 | mg/dL | Urinary chloride | 42 | mEq/L |
| Protein | (1+) | | Phosphate | 3.9 | mg/dL | FENa | 1.0 | % |
| Glucose | (−) | | Total cholesterol | 183 | mg/dL | FEUN | 36.0 | % |
| Occult blood | (±) | | Triglyceride | 148 | mg/dL | UP/Cr | 0.68 | g/gCr |
| Red blood cell | 1-5 | HPF | HDL-cholesterol | 32.1 | mg/dL | Urinary BMG | 45,027 | μg/L |
| White blood cell | 1-5 | HPF | LDL-cholesterol | 121.3 | mg/dL | Urinary NAG | 22.34 | U/L |
| Cast | (-) | | Glucose | 183 | mg/dL | UNAG/Cr | 29.59 | U/gCr |

PTT: activated partial thromboplastin time, BMG: beta 2-microglobulin, FENa: fractional excretion of sodium, FEUN: fractional excretion of urea nitrogen, HDL: high-density lipoprotein, HPF: high-power field, LDL: low-density lipoprotein, MCHC: mean corpuscular hemoglobin concentration, MCV: mean corpuscular volume, NAG: N-acetyl-beta-D-glucosaminidase, PT-INR: international normalized ratio of prothrombin time, UP/Cr: urinary protein/creatinine ratio

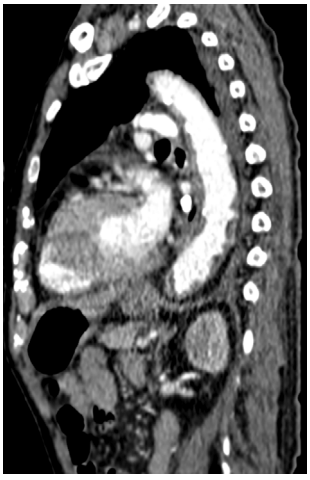

**Figure 2. Contrast-enhanced computed tomography, which was performed during a previous hospitalization, revealed multiple plaques in the thoracic aorta.**

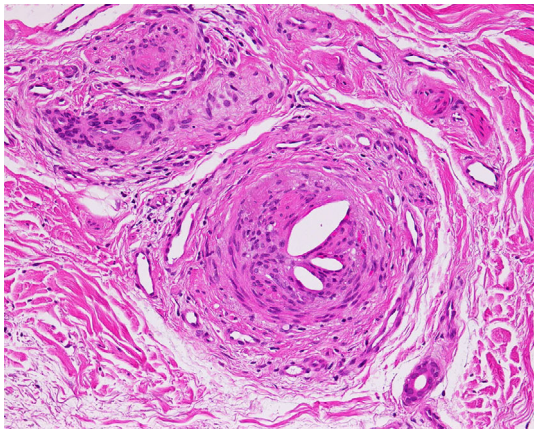

**Figure 3. A skin biopsy of the right toe revealed needle-shaped clefts in the lumen of the arterioles (Hematoxylin and Eosin staining; original magnification ×200).**

Although he had an almost completely normal kidney function [estimated glomerular filtration rate (eGFR) ranged from 60 to 110 mL/min/1.73 $m^2$] during his first admission, his kidney function had gradually decreased after discharge, and he was therefore re-admitted with renal failure and general fatigue.

On admission, his blood pressure was 128/49 mmHg, his heart rate was 75 beats per min, and his temperature was 37.1℃. Physical examination revealed no livedo reticularis, but blue-colored bilateral toes (Fig. 1), although the pulses in his bilateral pedal arteries were palpable. Laboratory data indicated azotemia, eosinophilia, iron deficiency anemia, hypoalbuminemia, and elevated C-reactive protein (Table). Chest X-ray revealed right-sided pneumonia and fecal occult blood was positive. We started antibiotics for pneumonia and a proton pump inhibitor for occult gastrointestinal bleeding without performing gastrointestinal endoscopy, as we were concerned about potentially exacerbating the patient's pneumonia.

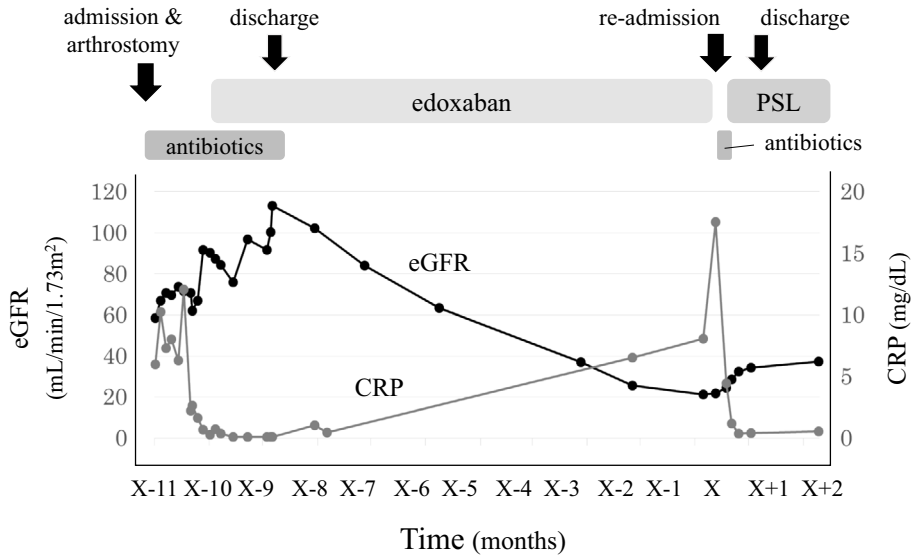


**Figure 4. The patient's clinical course. The patient's levels of eGFR (black line) gradually decreased about 1 month after starting edoxaban and gradually recovered after it was stopped and low-dose prednisolone was started. CRP: C-reactive protein, eGFR: estimated glomerular filtration rate, PSL: prednisolone**

Regarding azotemia, urinary chemistry suggested renal tubular injury. Drugs taken before re-admission were acetaminophen, azilsartan, benidipine, cetirizine, loxoprofen, rebamipide, sennoside, and edoxaban. Although loxoprofen is known to be a cause of renal tubular injury among these particular drugs, loxoprofen was started about 1 month before re-admission. The other drugs, except for edoxaban, were not started during the first admission. Contrast-enhanced computed tomography, which was performed during a previous hospitalization, revealed multiple plaques in the thoracic aorta (Fig. 2). The patient underwent no vascular procedures between the first and second hospitalization. In addition, skin biopsy of the right toe revealed needle-shaped clefts in the lumen of the arterioles, which is a characteristic finding of CCE (Fig. 3). Perivascular and intravascular inflammatory infiltrate including eosinophils indicative of vasculitis syndrome was not identified in the specimen. Because the patient's kidney function continued to decline since edoxaban was started, we diagnosed this case to be CCE caused by edoxaban and stopped the administration of the drug. A low-dose corticosteroid (prednisolone, 15 mg/day) was initiated after recovery from pneumonia with oral antibiotics. Thereafter, his blue-colored toes, azotemia, and eosinophilia gradually improved, and he was later successfully discharged (Fig. 4).

## Discussion

CCE is a systemic disease caused by the occlusion of arteries resulting from the embolization of atheromatous debris including fibrin, platelets, cholesterol crystals, and calcium fragments (1). The atheroemboli typically occlude small arteries of the extremities, brain, eye, kidney, or mesentery. Catheter or surgical manipulation of the aorta is a major cause of CCE, and anticoagulants or thrombolysis might precipitate CCE. Several cases of spontaneous CCE have been reported (2-4). Because invasive vascular procedures were not performed, CCE in this patient was thought to have been induced by anticoagulant therapy for DVT using edoxaban, which is one of the direct factor Xa inhibitors. To the best of our knowledge, there are no reports that Xa inhibitors can cause CCE.

The mechanism behind anticoagulant-induced CCE is not clear; however, several theories have been suggested. One plausible explanation based on an autopsy examination is that anticoagulants lead to CCE by hemorrhaging atherosclerotic plaques, by impairing the healing of ulcerated plaques (7, 8), or by dissolving fibrin clots that stabilized the atheroma in place (9-11).

Factor Xa inhibitors are a relatively new type of anticoagulant, as is the direct thrombin inhibitor dabigatran. Recently, Xa inhibitors and dabigatran have been collectively called DOAC in English (direct oral anticoagulants). DOAC have been reviewed and found to be non-inferior to warfarin for the prevention of ischemic stroke and systemic embolism, and is associated with a reduced incidence of hemorrhagic events (12, 13). There are a number of meta-analyses suggesting that DOAC pose a risk for bleeding comparable with warfarin (14, 15). Further study is therefore needed to clarify the bleeding risk from DOAC (16). There is no doubt, however, that DOAC are associated with a greater risk for bleeding than a placebo, therefore, it is possible that DOAC could be a cause of CCE by hemorrhaging atherosclerotic plaques.

Two case reports suggest that warfarin-induced CCE can be successfully treated using Xa inhibitors; with fonda-

parinux in one case (5) and with apixaban in the other (6). In these reports, it was noted that warfarin had a direct toxic effect on the capillaries, resulting in vasodilation and increased permeability (17). Although warfarin may pose a greater risk for inducing CCE compared with other anticoagulants (as mentioned in the suggested theory above), Xa inhibitors may have a weak ability to cause CCE indirectly via the bleeding of atherosclerotic plaques. Our findings suggest that edoxaban use is the only possible cause for CCE in the present case.

Regarding the optimal treatment for CCE, azotemia and symptoms are not always reversible even after removing the cause. From a cited case report (5), only six cases improved upon stopping warfarin among 13 reported warfarin-induced CCE cases. Therefore, it is difficult to reach any conclusions through observation by only stopping the suspected causative drug for drug-induced CCE. Although no definitive treatment has yet been established for CCE, the possible benefits of corticosteroids have been reported in a small series of cases (18-20). Therefore, we used corticosteroids for the treatment of CCE in this patient.

## Conclusion

CCE can be caused by edoxaban, one of the Xa inhibitors, as well as warfarin and other anticoagulants. Close attention should thus be given to a patient's kidney function and the skin findings of the feet and toes during the use of all types of anticoagulants, including Xa inhibitors.

**Author's disclosure of potential Conflicts of Interest (COI).**
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