Dear editor:

Cholesterol crystal embolism (CCE), characterized by diverse clinical presentation, limited therapeutic options and poor long-term outcomes, is a multisystemic disease in which cholesterol crystals emboli released from atherosclerotic plaques of the aorta or other major arteries occlude small arteries and subsequently lead to a foreign-body giant cell granuloma inflammatory reaction. Invasive vascular procedure, such as manipulation of the aorta during angiography or vascular surgery, is considered to be the main cause of CCE. It has also been reported to occur after thrombolysis or anticoagulants. Furthermore, CCE can be spontaneous. CCE involves multisystem organ dysfunction, such as kidney, skin, gastrointestinal tract, eyes and central nervous system, in which renal insufficiency has been found to be a main complication of CCE. In this case report, we describe a patient who suffered acute renal injury (stage 3) and renal artery stenosis caused by CCE after coronary stenting.

A 69-year-old male was hospitalized with acute renal injury (stage 3) in June 2019. Two months before visiting our hospital, he had undergone coronary angiography due to unstable angina, which was performed through the left femoral artery and showed 95% blockade in the right coronary artery, and then was advised to undergo coronary stenting in a local hospital. The serum creatinine level was within normal range before and one day after the procedure. One week later, blue-colored bilateral toes of the both feet were found and serum creatinine level was 122.6 μmol/L. Three weeks after the procedure, serum creatinine level was elevated to 223.1 μmol/L. Subsequently, a progressive aggravation in renal function was observed, accompanied with nausea, retching, oliguria (400 mL/d), chest tightness and shortness of breath, for which hemofiltration was performed by a local hospital. In terms of medical history, he had a history of hypertension and received oral medication. He did not have any drug-allergy history until admission. Prior to admission in our hospital, he had been smoking about 20 cigarettes/day and drinking heavily for 40 years.

Upon admission, physical examination revealed that his blood pressure was 160/80 mmHg, heart rate 88 beats/min, breath 20 times/min and temperature 36.7 °C. In addition, blue toes on both feet were noted (Fig. 1A) which felt cold to touch. Livedo reticularis was not found, and the pulses in his bilateral pedal arteries were palpable. Arterial blood gas analysis revealed severe metabolic acidaemia (pH 7.266, PO₂ 135.8 mmHg, PCO₂ 16 mmHg, BE -19.86 mmol/L). Urinalysis revealed significant proteinuria (3+) and microscopic haematuria (2+). Serum levels of creatinine (433 μmol/L) and urea (17.83 mmol/L) were increased, with a significant increase in high sensitive-C-reactive protein (hs-CRP) (23.41 mg/L). The ratio of eosinophil was 8%, with reduced hemoglobin (7.0 g/dL). Serum lipid levels showed that triglyceride was 1.96 mmol/L. Slight increases in D-dimer (12.73 mg/L), fibrin degradation product (38.64 mg/L) and activated partial thromboplastin time (65.8 s) were observed with an coagulation system test. Serum level of complement 3 (C3) was decreased (0.49 g/L). A 24-hour urine test revealed a total protein level of 2899.8 mg/24h. Serum level of B-urine natriuretic peptide...
(BNP) was 364 pg/mL. Erythrocyte sedimentation rate increased to 83 mm in the first hour.

Renal ultrasonography showed increased renal echogenicity, a low blood flow rate and a significant increase in the resistance in renal artery. Double pneumonia was confirmed by CT chest. GFR, examined by emission computed tomography (ECT), was 22.8 mL/min/1.73m². Computed tomography angiography (CTA) was performed to investigate vascular occlusion and plaque formation in the aorta and widespread erosive lesions and plaques in aorta were revealed. Of note, there was significant stenosis (90%) at the beginning of the right renal artery and slight stenosis (30%) at the beginning of the left renal artery (Fig. 1B). Fundus examination showed several yellow-white-colored patches in retina and a yellow-white-colored embolus in the fundus arteriole of right eye (Fig. 1C). After stabilization, renal biopsy was performed, which revealed cholesterol clefts in renal interstitium with foreign-body giant cell infiltration (Fig. 1D). Electron microscopy found diffusely fused podocyte foot processes and interstitial edema (Fig. 1E). A skin biopsy on his right toe was performed which revealed cholesterol clefts surrounded by multinucleated giant cells in the arteriole (Fig. 1F). Therefore, cholesterol crystal embolism was diagnosed.

After admission, hemodialysis (using nadroparin calcium as a general anticoagulant during HD) was performed to treat uremia and prevent congestive heart failure. Atorvastatin was administered at 40 mg/day to stabilize the atherosclerotic plaques through their lipid-lowering and anti-inflammatory properties. In order to reduce the reactive inflammatory response caused by cholesterol crystals emboli, oral prednisolone was administered at a low dose of 10 mg/day after recovery from pneumonia with antibiotics, as we were concerned that a higher dosage might potentially exacerbate the patient's pneumonia. CTA revealed significant stenosis (90%) at the beginning of the right renal artery. In response, stenting was performed in right renal artery to improve blood perfusion and renal function. Continuous hemofiltration was performed after the procedure. To treat uncontrolled hypertension of the patient, 3 different classes of antihypertensive drugs were prescribed (nifedipine controlled release tablets 3 mg BID; trichlorothiazide tablets 25 mg QD; carvedilol tablets 12.5 mg QD). After the combination therapy, the level of hs-CRP (1.27 mg/L) and eosinophilia (2%) were normal, blue-colored toes gradually improved, and renal function was partially restored with GFR at 24.7 mL/min/1.73m² and serum creatinine 293.29 μmol/L. Three months later, residual renal function showed a gradual and partial recovery. GFR until last visit was 25.3 mL/min/1.73m², serum creatinine was 201.52 μmol/L. (Fig. 1G)

CCE is a multi-systemic organ dysfunction, which is caused by the occlusion of small arteries by cholesterol crystal emboli released from eroded atherosclerotic plaques of the aorta, and thereby leads to a variety of clinical manifestations depending on the specific organ affected by emboli. CCE has been reported to occur spontaneously, recognized to be an iatrogenic complication from an invasive vascular procedure (catheter or surgical manipulation of aorta) or anticoagulants/thrombolysis therapy. The anatomical proximity of the kidneys to the abdominal aorta and degree of renal blood flow make the kidney a frequent target organ for CCE.

The exact mechanism underlying CCE is yet to be fully understood. Tissue injury and necrosis caused by CCs directly through mechanical obstruction that leads to vascular obstruction, tissue ischemia and cell necrosis, was the main factor in the pathogenesis of CCE. Endothelial inflammatory response has been reported to be another important mechanism. Crystal emboli released from eroded atherosclerotic plaques of the aorta elicitation endothelial injury and an early histiocytic response, including neutrophils and eosinophils infiltration in the early phase. Subsequently, a foreign-body giant cell reaction occurs and results in the engulfment of the cholesterol crystals. Ultimately, inflammation leads to endothelial proliferation, intravascular thrombosis and fibrosis. Studies have indicated that crystal emboli induce the activation of interleukin-1β (IL-1β) through the Syk, PI3K and NLRP3 inflammasome signaling pathway, and thereby lead to inflammatory reaction. Furthermore, activation of renin-angiotensin-aldosterone system (RAAS) and complement activation are also involved in the development of CCE. Activation of RAAS caused by CCE would lead to apoptosis, inflammation and fibrosis through oxidative stress, as well as vascular and tissue remodeling, thereby contributing to chronic kidney disease.

In addition, CCE activation of complement mediates the release of pro-inflammatory cytokines and inflammatory responses. CCE can lead to variable degrees of nonspecific clinical manifestations which may range from subtle to catastrophic. Skin and kidneys are the most common organs affected by CCE and their manifestations are often used as clinical diagnostic criteria for CCE. Clinical signs on the skin include blue toes syndrome, normal peripheral pulses and reddish-violet reticular discoloration of the lower limbs as a result of blood flow...
Fig. 1. Blue-colored toes of the both feet (A). Computed tomography angiography revealed widespread erosive lesions and plaques in aorta, significant stenosis (90%) in the right renal artery and slight stenosis (30%) in left renal artery (B). Fundus examination showed several yellow-white-colored patches in retina and a yellow-white-colored embolus in the fundus arteriole of right eye (C). Renal biopsy revealed needle-shaped cholesterol clefts deposits in renal interstitium with foreign-body giant cell infiltration (D). Electron microscopy revealed diffusely fused podocyte foot processes and interstitial edema (E). Skin biopsy of the right toe revealed needle-shaped cholesterol clefts surrounded by multinucleated giant cells in the arteriole (F). The clinical course in the patient after coronary stenting (G).
interruption in the dermal arteries due to spasm, inflammation or vascular obstruction. Renal complications of CCE presents as a sudden or continuous decline in renal function resulting from abrupt rupture of unstable plaques, accompanied with concomitant worsening of hypertension due to increased RAAS. 28%–61% of patients would need dialysis with partial recovery expected in 20%–30% of them. In addition, CCE also manifests as an abdominal pain/hemorrhage due to mucosal ulceration, ischemia, infarction and perforation as well as pancreatitis, acalculous cholecystitis, adrenal insufficiency and pulmonary embolization. In our patient, typical blue toes syndrome and progressively worsening renal function were manifested.

Histologically, the characteristic lesion of CCE is presence of cholesterol crystals (CCs) in the lumen of a blood vessel. The diagnosis of CCE is made by kidney biopsy with sensitivity of about 75%, which shows an occlusion of CCs in the lumina of arcuate, interlobular arteries, and glomeruli with a perivascular foreign-body giant cell and eosinophils infiltration. The emboli of CCs are generally defined by empty, biconvex, and needle-shaped clefts, since CCs usually dissolve during routine histologic preparation procedures. Podocyte foot processes injury, focal segmental glomerulosclerosis, interstitial fibrosis and tubular atrophy were found in the later stages of the disease. Generally, immunofluorescence staining for immunoglobulin A (IgA), IgG, IgM, C3, C1q, fibrin, kappa and lambda light chains is negative. Skin, muscle or gastrointestinal biopsies also provide evidence of CCE. Skin biopsy is less invasive and serves as an alternative to renal biopsy in nearly 90% of CCE cases. The case reported in this paper was histologically proven as CCE, in which both kidney and skin biopsies were performed and needle-shaped clefts deposits and foreign-body giant cell infiltration were observed.

Among many diagnostic challenges, contrast-induced acute renal injury (CI-AKI) was the common deceptive condition in early acute form of CCE induced renal insufficiency, especially in diabetic patients with renal insufficiency. CI-AKI is classically defined as a decline in kidney function within the first 48–72h following contrast administration, in the absence of alternative etiologies. Systemic vasculitis is another cause of confusion with sub-acute form of CCE with skin involvement, fever, laboratory evidence of inflammation and high eosinophil counts. The availability of anti-neutrophil cytoplasmic antibodies makes this confusion unlikely. Renal artery atherosclerotic stenosis and hypertensive nephrosclerosis have often been mistaken for delayed or chronic form of CCE.

There is no specific therapy for CCE. In order to prevent the progression of tissue ischemia or provide supportive care in the event of renal failure, various non-specific therapies have been attempted, including treating underlying heart failure and hypertension, nutritional support and renal replacement therapy if needed. Peritoneal dialysis, hemofiltration or hemodialysis has been shown to be adequate means of managing renal failure in such patients. Statins have been found to decrease the incidence of plaque rupture by reducing matrix metalloproteinase expression in atheromas and leading to an increase in fibrous cap thickness through collagen accumulation, and thereby improve renal outcome. A retrospective analysis of patients with severe aortic atherosclerosis has reported that the use of statins was associated with protective effect on atheroembolic recurrence rate. Moreover, statins have been found to reduce the serum level of CRP. Oral prednisolone at 1 mg/kg/day has proved helpful in restoring renal function and improving clinical outcomes by reducing reactive inflammatory response along with atheroembolization. However, the effects of steroids remain controversial. Some studies have indicated that corticosteroids did not have a favorable effect on long-term renal outcomes and were even associated with an increased risk of mortality. Anticoagulants should be avoided since they potentiate the problem. Therefore, we used statin, corticosteroids and hemodialysis for the treatment in this patient, accompanied with anti-hypertensive therapy and nutritional support. In particular, in order to improve blood perfusion and renal function, stenting was performed in right renal artery to treat renal artery stenosis.

Prognosis is generally considered poor. The major cause of death is not the consequence of renal failure but of concomitant visceral ischemia, especially in patients with severe necrosis in the brain, coronary arteries, spinal cord, mesentery, and/or pancreas, irrespective of the degree of renal failure. Renal outcomes are variable, with some patients requiring
maintenance dialysis and others showing improvement in renal function but with varying degrees of residual chronic kidney disease.

Conflicts of interest

None.

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