—Case Reports—

A Patient with Idiopathic Cholesterol Crystal Embolization: Effectiveness of Early Detection and Treatment

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Abstract

A 72-year-old man was admitted to our hospital because of progressive renal dysfunction persisting for 1.5 months. Physical examination showed livedo reticularis of the toes of both feet, peripheral edema, and gait disturbance due to the toe pain. The levels of blood urea nitrogen (50.0 mg/dL) and creatinine (2.81 mg/dL) were elevated, and eosinophilia (10%, 870/μL) was noted. A biopsy of the area of livedo reticularis revealed cholesterin crystals. The patient had not undergone angiography, anticoagulation therapy, or antithrombotic treatment. Idiopathic cholesterol crystal embolization was diagnosed. Transesophageal echocardiography revealed intimal thickening of the aorta and plaque. Oral steroid therapy was started because of the progressive renal dysfunction. After steroid therapy, the symptoms improved. Early diagnosis and treatment are important. Renal dysfunction is a common symptom in elderly patients. Cholesterol crystal embolization should also be considered as a cause of unexplained renal dysfunction, especially in such patients.
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Key words: livedo reticularis, eosinophilia, renal dysfunction

Introduction

Cholesterol crystal embolization (CCE) develops because of peripheral artery occlusion caused by needle-shaped cholesterin crystals detached from destroyed atheromatous plaques or fibrin microthrombi[1]. The major clinical findings of CCE are: 1) livedo reticularis (particularly of the toes), 2) rapidly progressive renal dysfunction, and 3) eosinophilia. In addition, various other clinical findings have been reported[1]. In particular, CCE developing in the toe arteries is often called "blue toe syndrome" because of the characteristic skin color[2]. Blue toe syndrome is accompanied by toe necrosis or renal failure, as a possibly fatal complication[2]. CCE is secondary or, rarely, idiopathic[1,3–5]. Secondary CCE is classified as that associated with endovascular manipulation, such as endovascular catheter manipulation and vascular graft replacement, or as that associated with anticoagulation/thrombolytic therapy. Definitive diagnosis requires biopsy of the area of livedo reticularis and renal biopsy. Because CCE has a poor

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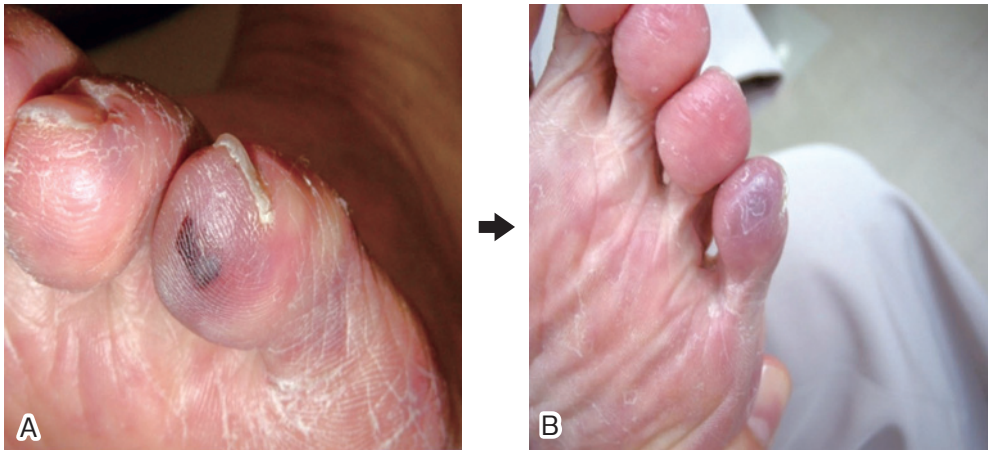

Fig. 1 Changes in livedo reticularis
The symptom of livedo reticularis improved after steroid therapy.
A: on admission, **B**: on discharge

Table 1 Results of Laboratry Tests

Blood (venus) Variable	Reference Range, Adults	data
red blood cell (×104/μL)	450–550	406
Hematocrit (%)	35–45	33.6
Hemoglobin (g/dL)	14–18	11.3
White-cell-count (×10^2/μL)	4,000–8,000	7,500
Eosinophils (%)	0.5–13	12.3
Platelet count (×10^4/μL)	20–40	23.2
Sodium (mEq/liter)	135–150	138
Potassium (mEq/liter)	3.5–4.3	4.9
Chloride (mEq/liter)	96–107	100
Urea nitrogen (mg/dL)	7–20	50
Creatinine (mg/dL)	0.6–1.2	2.81
Total protein (g/dL)	6.7–8.5	7.7
Albmin	3.8–5.5	4.1
Total Cholesterol (mg/dL)	130–220	218
triglyceride (mg/dL)	30–150	102
β2-mycrogloburin (mg/L)	1.0–1.9	6.4
C-reactive protein (mg/dL)	0.3≧	2.59
*MPO-ANCA	<10	<10 EU
**PR3-ANCA	<20	<10 EU
antinuclear antibodies	<20	(−)
Urine		
pH		5.5
SG		1.01
protein (g/day)		0.2
sugar (g/day)		0.1
ketone		(−)
Sodium (mEq/liter)		80.3
Potassium (mEq/liter)		17
Chloride (mEq/liter)		77.7
squamous epithelium (/HPF)		<1
transitional epithelium (/HPF)		<1
urinary cast		(−)

*MPO-ANCA: Myeloperoxidase-anti-neutrophil cytoplasmic antibody
**PR3-ANCA: Proteinase 3-anti-neutrophil cytoplasmic antibody

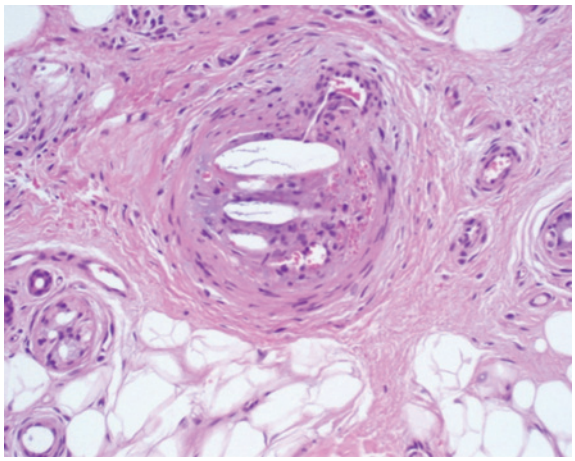

Fig. 2 A biopsy specimen of the patient
A biopsy of the area of livedo reticularis revealed cholesterin crystals.

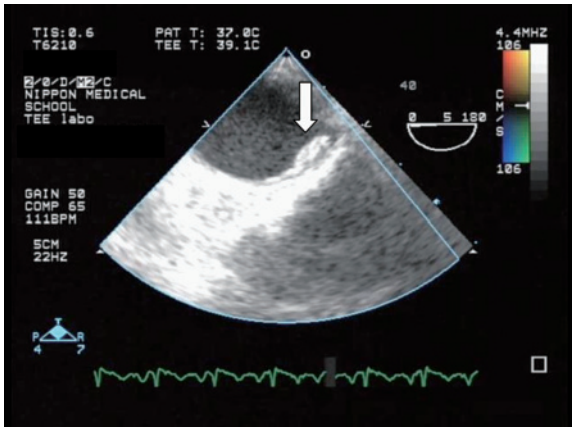

Fig. 3 Transesophageal echocardiograph of the patient
Plaque in the aorta **(arrow)**

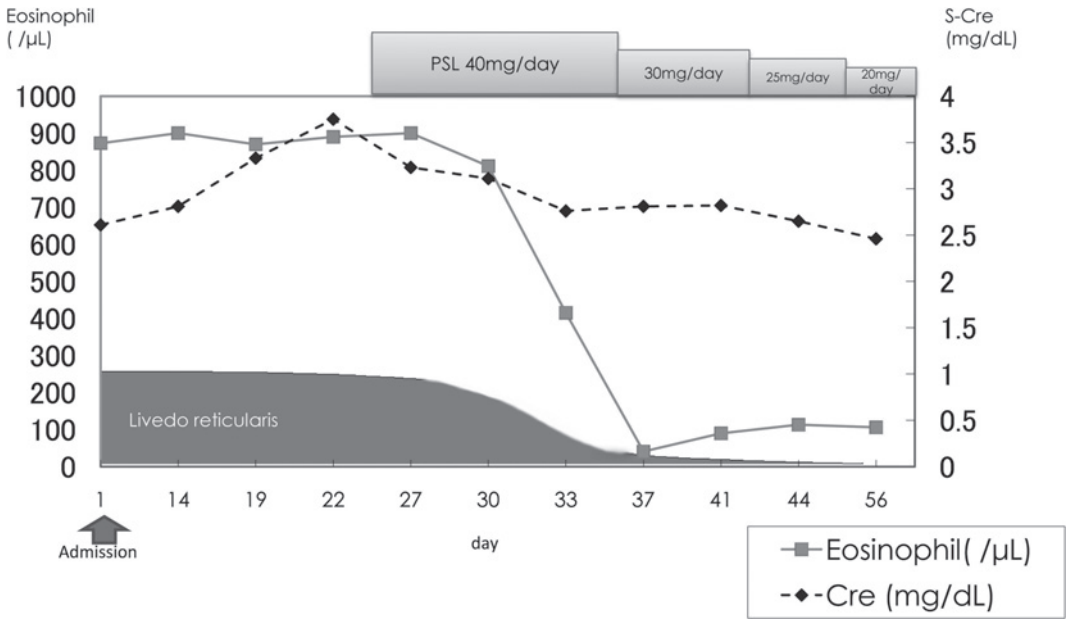

Fig. 4 Clinical course
S-Cre, serum creatinine, PSL, prednisolone

prognosis, early diagnosis and treatment are important. No specific or standard therapy for CCE has been established. The efficacy of steroid therapy has been controversial[1]. We report on a patient with idiopathic CCE who responded to steroid therapy.

Case Report

A 72-year-old man visited our department because of progressive renal dysfunction for 1.5 months and was admitted for examination and treatment. On admission, he showed livedo reticularis of the toes of both feet (**Fig. 1**), edema of the legs, eosinophilia (10%, 870/μL, and increased levels of blood urea nitrogen (BUN; 50 mg/dL) and creatinine (2.81 mg/dL), indicating renal dysfunction. He also complained of difficulty walking because of pain. The patient's history included surgery for papillary thyroid cancer with a favorable postoperative course at the age of 71 years but no renal dysfunction, hypertension, hyperlipidemia, or diabetes mellitus; the family history showed nothing of note.

On admission, the patient was 161 cm tall and weighed 58.2 kg. The body temperature was 36.9℃, and the pulse was regular at 88 beats per minute. The blood pressure was 172/98 mmHg. Physical examination showed no abnormalities except livedo reticularis of the toes of both feet. Chest and abdominal X-ray examinations revealed nothing of note. Blood biochemical and urinary analyses showed abnormal values (**Table 1**). He complained of severe pain in the feet and difficulty in walking, in addition to livedo reticularis of the toes of both feet. Skin biopsy confirmed the embolization of a vessel immediately below the epidermis by cholesterin crystals, and a definitive diagnosis of CCE was made (**Fig. 2**).

Abdominal magnetic resonance angiography showed no clear stenosis of the bilateral renal arteries, whereas abdominal computed tomography and transesophageal cardiac ultrasonography identified a plaque (a few millimeters thick) in the abdominal aorta (**Fig. 3**). Five days after admission, because of increases in the levels of BUN (43.9 mg/dL) and creatinine (3.3 mg/dL), oral steroid therapy (prednisolone, 40 mg/day) was started. Six days after the start of this treatment (12 days after admission), the BUN and creatinine stopped increasing (**Fig. 4**), and the pain in the toes and the difficulty in walking also decreased. Subsequently, the renal function gradually improved, and, 35 days after the start of oral steroid therapy, the BUN and creatinine levels had decreased to 34.6 mg/dL and 2.46 mg/dL, respectively, and partial disappearance of the livedo

reticularis of the toes and a decrease in the eosinophil count were also observed (**Fig. 1 and 4**). The patient's general condition was favorable, and there were no findings suggesting infection. He was discharged 36 days after admission (prednisolone: 20 mg/day).

To date, the patient has been followed up on an outpatient basis with a gradual reduction in the steroid dose. Neither aggravation of the renal function nor new livedo reticularis has been observed.

Discussion

About 80% of cases of CCE have been reported to occur because of catheter manipulation and anticoagulation therapy[3–5]. In the present patient, there was no history of endovascular catheter manipulation or anticoagulation or thrombolytic therapy, and, on the basis of the symptoms and the results of a skin biopsy, a diagnosis of CCE was made. Administration of a steroid alone was effective; its relatively early start may have led to a favorable outcome.

CCE is part of a multisystemic disease caused by occlusion of small arteries by cholesterol crystal emboli derived from ulcerated atherosclerotic plaques[4]. Depending on the location of the atherosclerotic plaques releasing these cholesterol fragments, one may see cerebral transient ischemic attacks, livedo reticularis of the lower extremities, Hollenhorst plaques in the retina with visual field losses, necrosis of the toes, and acute glomerular capillary injury[1]. Irregular emboli trapped in the microcirculation cause microcrystal angiitis, characterized by infiltration of polymorphonuclear leukocytes and eosinophils to affected arterioles, preceding mononuclear-cell infiltration and giant-cell formation[1,4]. This endothelial inflammatory reaction causes tissue ischemia and ultimately leads to the failure of various organs, including the kidneys. The pathogenesis of renal failure due to CCE is thought to involve the reactive inflammation surrounding the cholesterol crystals, which leads to luminal occlusion[6]. Steroids might be able to reduce the inflammation and have been shown by several studies to be beneficial[7,8]. However, other studies have shown no significant benefit from steroid treatment[9,10]. Thus, steroid use remains controversial, although it might play a role in patients with multisystem inflammation.

There is no established treatment for CCE. The main aim of treatment is to prevent recurrent embolism. When CCE is diagnosed, anticoagulation therapy is discontinued. Successful treatment with statins has been reported in some cases[5,9,11]. Statin therapy has a beneficial effect when started after CCE has been diagnosed. Statins stabilize plaques in the aorta, and attention has been directed to their usefulness[1]. For symptom management, hypertension and cardiac and renal failure should be aggressively treated. Because of the high case-fatality rate, treatment should be started early when CCE is suspected.

In the present patient, transesophageal cardiac ultrasonography showed plaques that were possible sources of emboli. This examination, which can also confirm plaques of the aortic wall and the state of cholesterin (whether it can scatter), is useful for preventing CCE.

Progressive renal dysfunction is often encountered in clinical practice. In particular, in elderly patients with decreased renal functional reserve, renal blood flow decreases owing to mild dehydration, a decrease in blood pressure, or the administration of nonsteroidal anti-inflammatory drugs, readily inducing renal dysfunction. When renal dysfunction of unknown cause is observed, differentiation among conditions, including the above causes as well as CCE, is important and may lead to early detection and treatment.

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