Clinical Characteristics and Outcomes of Chinese Patients with Cholesterol Crystal Embolism after Coronary Intervention

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Summary

Background: Cholesterol crystal embolism (CCE) is a complication of atherosclerosis. Vascular surgery, vascular angiography, and anticoagulation have been identified as inciting factors.

Hypothesis: This paper sought to analyze the clinical characteristics of patients with CCE after percutaneous coronary intervention.

Methods: Six patients with atherosclerosis presenting with simultaneous occurrence of acute renal failure and peripheral ischemic changes were diagnosed with CCE and their clinical data were analyzed.

Results: The average age of the patients was 72 years. Most had risk factors of atherosclerosis such as hypertension, diabetes, and smoking. The levels of serum creatinine increased progressively after coronary angiography. All patients had concomitant skin lesions, including blue toes. Cholesterol crystal emboli were found in arterioles by cutaneous biopsy in one patient. All patients received statins and two of these received dialysis therapy. Three patients died and three remained in chronic renal failure.

Conclusion: Since CCE is a severe complication of coronary intervention, special attention should be paid to this disease.

Key words: cholesterol crystal embolism, renal failure, coronary angiography

Introduction

Cholesterol embolism is a multisystem disease resulting from cholesterol crystal embolism (CCE) to multiple organs,

including kidney, skin, brain, eyes, gastrointestinal tract, and extremities. Cholesterol embolism may occur spontaneously or secondary to endovascular trauma such as vascular surgery or angiographic procedures. Other etiologic factors include anticoagulation and thrombolysis therapy.¹ The proximity of the kidney to the abdominal aorta and the rich renal blood supply make the kidney a frequent target organ for atheroemboli.

The prevalence of cholesterol embolism is not known. Estimated incidence of clinically detectable cases amounted to 3%,² but retrospective autopsy or biopsy studies may exaggerate the frequency of the disease because these may detect subclinical cases. As the morbidity of atherosclerosis increases and angiographic or vascular surgical procedures known to induce this disease are now in widespread use in many hospitals, CCE may become more prevalent in the coming years. Cholesterol crystal embolism is a serious disease with high mortality, but its clinical manifestations are frequently ignored by doctors in China. In this study, we report six cases with CCE diagnosed at our institution that occurred after percutaneous coronary intervention in the past 3 years.

Methods

According to the criteria of Scolari *et al.*³ with some revisions, patients were diagnosed with CCE at Peking University First Hospital from October 2003 to January 2006. All patients met the following criteria: (1) acute renal failure occurring in elderly subjects with extensive atherosclerotic vascular disease; (2) simultaneous occurrence of ischemic changes to extremities, including livedo reticularis, mottling, cyanosis, or gangrene of the toes. Acute renal failure because of contrast nephropathy or acute tubulointerstitial nephritis was excluded clinically.

The data of baseline information, clinical and laboratory features, and outcomes were collected.

This research was approved by the local ethics committee and informed consent of the patients was obtained.

Results

Demographic Feature

According to the above criteria, six patients (5 men, 1 woman, average age 72 years [67–79]) were diagnosed with CCE. The main clinical features of the patients are summarized in Table I.

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TABLE I Clinical features of the six patients with cholesterol crystal embolism

Patient No.	Age/sex	Initial diagnosis	Inciting event	Diabetes	Hypertension	Hyperlipidemia	Smoking
1	67/M	Angina	Coronary angiography	Yes	Yes	Yes	Yes
2	74/M	Angina	Coronary angiography and stenting	No	Yes	No	Yes
3	68/M	Angina	Coronary angiography and stenting	No	Yes	Yes	Yes
4	75/M	AMI	Coronary angiography	No	No	No	Yes
5	79/F	AMI	Coronary angiography, renal artery angiography, and stenting	Yes	Yes	No	No
6	69/M	Angina	Coronary angiography	No	Yes	Yes	No

Abbreviations: M = male, F = female, AMI = acute myocardial infarction.

Clinical and Laboratory Findings

All onsets of CCE were observed after coronary angiography (three patients also received coronary or renal artery intervention). The interval from the inciting event to the onset of CCE varied from 1 to 20 days. Usually, cutaneous lesions appeared before the onset of renal symptoms. Cutaneous manifestations of CCE, including digital mottling and cyanosis, occurred in all patients. Pedal pulses were often normal. The level of serum creatinine increased progressively after onset of CCE. Urinalysis demonstrated mild proteinuria but lack of active cellular casts, hematuria, and leukocyturia. Antecedent hypertension exacerbated by the embolic disease was present in two patients (blood pressure rose from 140~150/80~90 to 170~175/100 mmHg). The laboratory findings are summarized in Table II.

Skin biopsies were performed on three patients. Cholesterol clefts were demonstrated in cutaneous and subcutaneous vasculature in only one patient.

Treatment and Outcome

All patients received statins, including simvastatin 20 mg/day, atorvastatin 10 mg/day, or pravastatin 20 mg/day. Renal function was followed up. Patient No. 1 has been receiving maintenance peritoneal dialysis since 2 months after onset, and urine volume has increased from 300 to 1000 ml per day. Patient No. 2 experienced a decline of serum creatinine to 2.04~2.15 mg/dl, but died of cerebral hemorrhage 1 month af-

ter discharge. Patient No. 3 received prednisone (30 mg/day) in addition to statin therapy. Prednisone was tapered to 15 mg/day 1 week later and was discontinued 1 month later. This patient was followed up for 5 months and the serum creatinine remained 2.94~3.05 mg/dl. Patient No. 4 was followed up for 2 months and the serum creatinine level decreased to 1.88~2.30 mg/dl. Patient No. 5 received emergent peritoneal dialysis during hospitalization because of acute renal failure and died 1 day later. The serum creatinine level of Patient No. 6 decreased to 4.36 mg/dl 2 weeks after treatment. He received coronary artery bypass graft due to recurrent angina but died of acute cardiac failure 1 day after surgery.

Discussion

Cholesterol crystal embolism is characterized by the occlusion of arterioles by cholesterol crystal emboli deriving from eroded atherosclerotic plaques in the aorta or large feeder arteries. The current study retrospectively analyzed the cases of 6 Chinese patients with CCE, based on the criteria of Scolari *et al.*³ describing the clinical, laboratory, and pathologic characteristics of this disorder. It was found that the occurrence of CCE in China may not be rare and is probably underdiagnosed. The increase of iatrogenic procedures performed in the hospital may contribute to the increasing prevalence of CCE. All patients in our study had confirmed coronary heart disease and underwent coronary angiography. The characteristics of our patients were similar to those reported in previous series.⁴ The risk factors of CCE were consistent with those of athero-

TABLE II Laboratory findings of the six patients with cholesterol crystal embolism (CCE)

Patient No.	Interval to onset of CCE (days)	Basal creatinine (mg/dl)	Highest creatinine (mg/dl)	Urine protein (mg/dl)	WBC ($\times 10^9/l$)	Eosinophils ($\times 10^9/l$)	ESR (mm/h)	CRP (mg/l)	Complement 3 (g/l)
1	1	1.33	13.57	75	12.96	1.07	23	43.2	0.80
2	2	1.24	2.60	30	10.9	0.36	UNK	UNK	UNK
3	20	1.36	4.46	100	9.18	0.62	23	10.8	UNK
4	20	0.79	4.56	30	10.5	1.57	108	9.22	0.84
5	10	1.43	6.67	Negative	5.38	0.48	55	9.54	UNK
6	2	1.81	6.31	50	14.86	5.25	65	UNK	UNK

Abbreviations: WBC = white blood count, ESR = erythrocyte sedimentation rate, UNK = unknown, CRP = high-sensitivity C-reactive protein.

sclerosis, including age >65 years, smoking, hypertension, and diabetes mellitus.

Because of the involvement of multiple organs, the clinical manifestations of CCE are extremely variable. In this study, using cutaneous and renal clinical manifestations as diagnostic criteria for CCE in the six cases, we found no lesions in other organs. In previous studies, cutaneous manifestations were found in 35–90% of patients with CCE, and renal clinical manifestations were found in approximately 50% of patients.⁵ In addition, cholesterol embolism at other sites may lead to gastrointestinal, neurologic, and ophthalmic manifestations.⁴ If manifestations of embolization occur in other areas, more patients might be diagnosed with CCE.

Laboratory investigation may offer further support to the diagnosis, but it lacks specificity. Urinalysis may show bland urine or proteinuria (1+ or more).⁶ Patients with CCE frequently have an elevated erythrocyte sedimentation rate, and eosinophilia was observed in 80% of the patients.⁷ Lye *et al.*⁸ found hypocomplementemia in 39% of the patients with renal atheroemboli. In our study, complement levels were normal in the two patients evaluated. Hypocomplementemia may be the result of complement activation by the atheromatous material. We considered that the absence of hypocomplementemia could be attributed to the delay of examination during the acute phase. It was also found that C-reactive protein (CRP) levels increased in most patients. A prospective study demonstrated higher CRP levels were associated with an increased risk of CCE.⁹

Diagnosis of CCE depends on biopsy of an affected organ. A typical lesion is the occlusion of affected arteriole lumen by biconvex needle-shaped cholesterol crystals (which dissolve during histologic processing to leave clefts).¹⁰ The diagnostic sensitivity depends on the biopsy organ. It has been reported that the sensitivity of a skin biopsy specimen was 41%, compared with 100% for a muscle biopsy and 75% for a renal biopsy.⁴ In our study, antiplatelet drugs could not be withdrawn in some patients due to coronary stenting and some patients were in a critical situation; therefore, none of the patients received renal biopsy. Three patients underwent skin biopsy, and intra-arteriolar cholesterol crystals were found in one patient. The sensitivity of skin biopsy is low; therefore, it was considered that the diagnosis could not be excluded even though no cholesterol crystals were found in the specimens.

All forms of treatment aim to halt the progression of tissue ischemia and prevent repeated showers of CCE; however, at present no effective method is available. Corticosteroids and statins may be beneficial,^{11, 12} however, no controlled studies have shown that medical treatment is helpful after occurrence of CCE. In the present cases, statins relieved symptoms and renal function improved partially. One patient received prednisone for 1 month, but his creatinine level did not improve noticeably. Two of our patients were treated with maintenance peritoneal dialysis. Theriault *et al.*¹³ demonstrated that peritoneal dialysis may be better than hemodialysis for the recovery of renal function, because the systemic anticoagulation used for hemodialysis may promote the atheroembolic process. However, more evidence would be needed to draw any firm conclusion.

The prognosis of patients with CCE is not optimistic. Scolari *et al.* reported a 1-year survival rate of 69%, with most patients dying of cardiovascular events, gastrointestinal ischemia, and stroke.^{3, 5} In our study, three of the six patients died within 2 months. It seems that the outcomes of Chinese patients with CCE are poorer than those reported in the literature. The mortality from CCE was associated with a high level of creatinine, the number of coexisting risk factors, and the history of peripheral vascular disease.¹⁴

Conclusion

Cholesterol crystal embolism should be considered when patients, especially the elderly, have acute renal failure after angiography or other vascular intervention therapy. In China, the incidence of CCE may not be very low, the prognosis is dismal, and the mortality may be relatively high. Large-scale investigations of the clinical characteristics and treatment of CCE in Chinese patients are needed.

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