Chronic Cholesterol Crystal Embolism with a Spontaneous Onset

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Abstract

A 74-year-old man was referred to our hospital because of hypertension, blue toe syndrome and an elevation of serum creatinine from 0.8 to 1.4 mg/dl for eleven months. He had no history of invasive vascular procedures. Atherosclerosis was initially suspected, but renal impairment was accelerated following anticoagulant therapy. A renal biopsy established the diagnosis of cholesterol crystal embolism. Withdrawal of anticoagulants and the combination therapy with LDL apheresis and corticosteroids led to stabilization of the renal function. In patients with risk factors for atherosclerosis, cholesterol crystal embolism should be included in the differential diagnosis of chronic kidney disease.

Key words: cholesterol crystal embolism, chronic kidney disease, renal biopsy, LDL apheresis, corticosteroid

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Introduction

Cholesterol crystal embolism (CCE) or atheroembolism is increasingly recognized as an iatrogenic complication after an invasive manipulation of the aorta or large arteries and after anticoagulant or fibrinolytic therapy, but it can occur spontaneously (1-6). Clinically, three types of renal functional impairment caused by CCE have been described: acute, subacute and chronic types (5). The chronic type is rare and frequently occurs without triggering events (5), with clinical features similar to those found in patients with ischemic nephropathy and nephrosclerosis, and may be missed if a renal biopsy is not performed. Here, we describe a patient of probably chronic CCE with a spontaneous onset, in whom the exacerbation of renal impairment due to anticoagulant therapy was examined in detail and a renal biopsy led to the definite diagnosis.

Case Report

In February 2006, a 74-year-old man was admitted to the department of vascular surgery in our hospital because of blue toe syndrome which had proven resistant to intravenous alprostadil injection over a four-month period. He had a history of smoking a pack per day for 51 years. His usual medication regimen included a statin and a low-dose aspirin. In April 2005 he was diagnosed with Stage 2 hypertension and was treated with calcium channel blockers, beta-blockers and angiotensin II receptor blockers. Despite multi-drug therapy his blood pressure was not within the normal range. Eleven months prior to admission, serum creatinine was 0.8 mg/dl (normal: 0.6-1.1 mg/dl), but had increased gradually to 1.4 mg/dl upon admission (Fig. 1). Physical examinations at the time of admission revealed cyanosis in the toes (Fig. 2) and an absence of palpable pedal and posterior tibial pulses bilaterally. Right and left ankle brachial pressure index was 0.86 and 0.99, respectively. Fundoscopy was normal. Enhanced magnetic resonance angiography using Gadolinium-DTPA showed irregular walls of the thoracic and abdominal aorta without an aneurysm (Fig. 3A), stenosis of bilateral external iliac arteries (Fig. 3B) and right anterior tibial artery, and obstruction of right fibular artery. Electrocardiogram revealed atrial fibrillation and left ventricular hypertrophy. Echocardiography showed mild dilation of the left atrium with no thrombi. At that time serum C-reactive protein and the peripheral blood picture were not examined. From these clinical findings, the diagnosis of arteriosclerosis obliterans was strongly suspected and warfarin was administered in addition to low-dose aspirin. The range of prothrombin time for international normalized ratio (INR) was between 1.6 and 2.1. Thereafter, the decline rate of

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reciprocals of serum creatinine (1/s-Cr) was accelerated from 0.043 to 0.070 dl/mg/month, and the serum creatinine rose to 2.1 mg/dl in May 2006. He was referred to our department. Laboratory examinations included urinalysis which was negative for proteinuria, occult blood, nor leukocyturia, a red blood cell count of 355×10^4/mm³, and a white blood cell count of 6,800/mm³ consisting of 7.4% eosinophils. Fasting blood glucose was within the normal range, but hemoglobin A1c was elevated to 5.9% (normal: 4.3-5.8%). Urinary excretion of β₂-microglobulin was elevated to 4,306 μg per day. The erythrocyte sedimentation rate was mildly elevated to 22 mm/h. Serum C-reactive protein was negative, and serum immunoglobulin fractions and complement levels were normal. Serum levels of total cholesterol, HDL-cholesterol, LDL-cholesterol and triglyceride were 159 mg/dl, 27 mg/dl, 104 mg/dl and 121 mg/dl, respectively. Anti-nuclear antibody was negative. Based on a suspicion of CCE, a skin biopsy was taken from the right great toe, but showed no abnormality (Fig. 4). Therefore, atherosclerotic renal lesion or chronic tubulointerstitial nephritis was suspected as the etiology of the renal impairment. In an attempt to clarify the etiology, a percutaneous renal biopsy was undertaken after discontinuing warfarin and aspirin. On light microscopy, diffuse interstitial fibrosis with tubular atrophy was observed (Fig. 5A). The 40 glomeruli examined revealed no abnormalities except for 2 collapsed glomeruli. Cholesterol crystal emboli consisting of clusters of elongated, biconvex, needle-shaped clefts were seen in the interlobular arteries (Fig. 5B). The lumen was narrowed by fibrosis and infiltrating cells surrounding the crystals and mild perivascular infiltration of mononuclear cells without eosinophils or multinucleated giant cells were observed. Interlobular arteries also showed intimal and medial thickening. Direct immunofluorescence showed no deposits of IgG, IgA or C3c in the glomerulus or interstitium.

From these histological findings, a definitive diagnosis of
CCE was made. In addition to the withdrawal of anticoagulants and the continuation of statins, aggressive treatments were performed. LDL apheresis using Liposorber LA-15 (Kaneka Corporation, Osaka, Japan) and exchanging approximately 3 L of plasma per session was initiated and a total of ten sessions were completed over 2 months. Prednisolone, 20 mg (0.3 mg/kg) per day was orally administered. Following these treatments, pain and cyanosis of toes improved. In July his serum creatinine decreased to 1.4 mg/dl. Serum levels of total cholesterol, HDL-cholesterol, LDL-cholesterol and triglyceride were 171 mg/dl, 43 mg/dl, 99 mg/dl and 132 mg/dl, respectively. Fasting blood glucose and hemoglobin A1c was 137 mg/dl and 6.0%, respectively. To date, with administration of amlodipine 5 mg per day, his blood pressure has been within the normal range. There has been no increase in his serum creatinine up to now with slow tapering of prednisolone.

**Discussion**

The histological renal lesions in the present patient showed clusters of elongated, biconvex, needle-shaped clefts in interlobular arteries which are typical of CCE. Although CCE is increasingly recognized as an iatrogenic complication after an invasive manipulation of the aorta or large arteries during angiography, angioplasty, or surgery, and after anticoagulant or fibrinolytic therapy (1-6), it can occur spontaneously in about 10% of cases (5, 6). Clinically, three types of atheroembolic renal disease have been described (5). In the first type, renal impairment may be abrupt and have a sudden onset within one to two weeks of a clear inciting event. The second type, the most frequently observed, is characterized by a subacute time course, in which renal impairment occurs in a stepwise fashion manifested by an increase in serum creatinine level a few weeks rather than a few days. The third clinical type, which is the least common type, presents as a chronic and stable renal impairment occurring spontaneously in contrast to the acute and subacute types which are usually initiated after a triggering event. In the chronic type, the true role of CCE in the progression of renal impairment is difficult to assess because CCE usually occurs in patients with co-existing angiosclerotic and atherosclerotic renal lesions (5). Although a renal biopsy leading to a definite diagnosis of CCE was performed after anticoagulant therapy and atherosclerotic lesions were also observed in the specimen, the principal cause of renal impairment before the therapy was thought to be CCE because of the finding of bilateral blue toes in the setting of renal impairment. CCE in our patient had no triggering events before the onset, that is, it spontaneously occurred. While there have been no reports regarding the significance of 1/s-Cr in patients with CCE, our patient’s rate of renal impairment before anticoagulant therapy may correspond to that of a chronic and stable type. The rate of renal impairment was accelerated and was changed to that of a subacute type by anticoagulants, which were administered due to impalpable pedal and posterior tibial pulses, decreased ankle brachial...
pressure index and the findings of magnetic resonance angiography which led to a strong suspicion of arteriosclerosis obliterans.

The identification of needle-shaped cholesterol clefts on the biopsy specimen is essential to establish the diagnosis of CCE. The skin, muscle and kidney were the three most common sites for obtaining a premortem diagnostic biopsy (1). The skin is an easily accessible site and the sensitivity is reported to be more than 90% if done repeatedly (1, 7), whereas renal histological examination may be inconclusive because CCE can be a patchy process. Especially in patients with a spontaneous and chronic onset the diagnosis of renal atheroembolism may be difficult to establish. In the present patient atherosclerotic renal lesion or chronic tubulointerstitial nephritis was suspected because of slow deterioration without proteinuria and no abnormal findings of the skin biopsy. Although our patient may be inadvertently diagnosed by renal biopsy, renal biopsy should be aggressively proceeded to confirm the diagnosis of the chronic type of CCE and to distinguish other diseases in patients clinically suspected of having CCE with negative skin biopsy findings and evidence of renal impairment.

Patients with CCE have been considered to have a poor overall prognosis (1–6). Scolari et al (6) reported that for the mean follow-up period of about five years end-stage renal disease and death occurred in 24% and 38%, respectively in a prospective study of 95 patients with atheroembolic renal disease. There are no large trials evaluating any medical therapies for the treatment of patients with CCE. Only statins may benefit by decreasing the risk of future embolization (6). There are isolated reports suggesting that corticosteroids (8–11) or LDL apheresis (10, 12) may be useful for patients with CCE following radiological interventional procedures. However, as yet, there have been no reports on the effect of corticosteroids or LDL apheresis in patients with a spontaneous type of CCE. Scolari et al (5) reported that in 32 out of 52 patients renal function slowly improved or stabilized by the general treatment characterized by the avoidance of anticoagulants and good control of hypertension. In the present patient there has been no increase in the serum creatinine concentration for 7 months after the medical treatments, but it is not entirely clear whether the improvement of renal function was induced by the withdrawal of anticoagulants or the combination therapy because they were undertaken at about the same time. A study with a large number of patients may give definite directions for the effectiveness of aggressive treatments for a spontaneous and chronic type of CCE.

In summary, we have described a patient of probably chronic CCE with a spontaneous onset and with an exacerbation by anticoagulant therapy. In patients with risk factors for atherosclerosis such as age, smoking, hypercholesterolemia, hypertension, obesity and diabetes, CCE should be included in the differential diagnosis of chronic kidney disease. Early diagnosis by renal biopsy may be an effective strategy for managing this disease.

References