Renal Cholesterol Embolic Disease Effectively Treated with Steroid Pulse Therapy

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Abstract

A 65-year-old man developed acute renal failure with eosinophilia two weeks after a coronary bypass operation and angiography. Renal biopsy revealed cholesterol crystal embolism (CCE) in glomeruli and arterioles. Low-dose corticosteroid therapy failed to recover the renal function; further deterioration of renal function and peripheral ischemic symptoms such as livedo reticularis and blue toes occurred. However, steroid pulse therapy successfully attenuated CCE-induced renal failure and eosinophilia. It is suggested that steroid pulse therapy might be effective to treat CCE-induced renal failure and eosinophilia could be a useful marker for activity of CCE.

Case Report

A 65-year-old Japanese man was diagnosed with hypertension 15 years previously and has been treated with anti-hypertensive drugs including amlodipine, prazocin and furosemide, since then. Two years previously, he started subcutaneous injection of insulin due to diabetes mellitus. Eight months ago, he presented with chest oppressive sense and coronary angiography revealed triple vessel disease. His renal function was within the normal range. Then coronary artery bypass grafting and follow-up coronary angiography were performed. Warfarin potassium administration was started and the levels of international normalized ratio (INR) has been maintained between 1.5 and 2.0. Two weeks after coronary angiography, renal failure suddenly appeared.

Blood pressure was 146/80 mmHg. Laboratory findings showed peripheral white blood cells 9,210/mm³, eosinophils 1,160/mm³ (12.6%), hemoglobin 9.4 g/dl, platelets 22.3x10^7/mm³ and total protein 6.6 g/dl. Liver enzymes were within normal ranges. Serum creatinine was 3.0 mg/dl and blood urea nitrogen was 37.2 mg/dl. Total cholesterol was 192 mg/dl and triglyceride was 239 mg/dl. Fasting blood glucose was 104 mg/dl and hemoglobin A1c was 6.5%. Urinary beta2-microglobulin was 68,850 μg/day. Urinary protein was 0.27 g/day. Urinary occult blood was not detected. C-reactive protein was 0.5 mg/dl. Serum immunoglobulin levels were within normal ranges (IgG 1,650 mg/dl, IgA 222 mg/dl, IgM 219 mg/dl). Hypocomplementemia was not detected. Autoantibodies to neutrophil cytoplasmic antigens were negative. Fundus examination showed mild arteriosclerotic changes without diabetic retinopathy.

Initially, interstitial nephritis was suspected because of the existence of eosinophilia, and prednisolone (20 mg/day p.o.) was administered. Although eosinophilia gradually subsided, renal function was not improved. Then, renal biopsy was performed. Light micrography revealed global sclerosis in 20 percent of glomeruli and most of remaining glomeruli...
showed mild mesangial accumulation resembling benign nephrosclerosis. However there were no other accompanying abnormalities, such as crescent formation. Of note, biconvex needle-shaped clefts due to CCE were found in the glomerular tufts and arterioles (Fig. 1). Tubules were focally atrophic and interstitium showed fibrotic changes. Immunofluorescence demonstrated no specific deposits. Based on these findings, we diagnosed that his renal injury was induced by CCE.

Anticoagulant, warfarin potassium, was discontinued because it was a risk factor for CCE. The oral steroid therapy was tapered and stopped in the outpatient department one month later because renal function did not show any improvement. However, soon after the termination of steroid, livedo reticularis, ischemia of toe, urine volume loss, general fatigue and foot edema occurred and he was admitted again.

Blood pressure was 140/60 mmHg. Laboratory findings showed white blood cells 8,480/mm³, eosinophils 1,970/mm³ (23.2%), total protein 5.6 g/dl, serum creatinine 6.5 mg/dl, C-reactive protein 0.7 mg/dl, urinary protein 0.23 g/day and negative urinary occult blood.

According to the clinical and laboratory findings, the recurrence of CCE was suspected and steroid pulse therapy (methyl-prednisolone 250 mg/day for two days) was started. After repeating pulse therapy once more, renal function was gradually recovered to 3.5 mg/dl serum creatinine. Eosinophilia and his general condition were also improved. During the steroid pulse therapy, the amount of insulin subcutaneous injection was increased to control blood glucose levels; diabetic complications, including retinopathy, hypertension and hyperlipidemia have not shown further deterioration so far. Although steroid was gradually tapered, his renal function has been maintained without the further progression of renal failure and eosinophilia for one year (Fig. 2).

Discussion

Cholesterol crystal embolism is a multisystemic disorder that generally affects many organs. It is often noted in patients with severe atherosclerotic change after anticoagulation and various types of arterial operations. Cholesterol crystals are dislodged from atherosclerotic lesions of the aorta or large feeder arteries and cause embolization mainly in vessels between 50 and 200 µm in diameter. Embolized crystals induce an inflammatory response and lead to permanent organizing occlusion of the artery (1).

The first case of renal CCE was reported by Flory in 1945 from the studies of autopsies (2). Although CCE can occur spontaneously, there are several triggering factors including vascular injury, angiographic procedure, anticoagulation and thrombolysis. Risk factors for CCE are older age (60 years or over), male sex, hypertension, diabetes mellitus and smoking. Anorexia, general malaise, pyrexia, pain of lower extremities, cutaneous findings (livedo reticularis, purple toes, gangrene), hypertension, renal failure, symptoms of eyes and gastrointestinal involvement are recognized as clinical manifestations (1). The characteristic features of CCE on laboratory findings include eosinophilia, an increased level of C-reactive protein and a high erythrocyte sedimentation rate (3).

In the present case, renal biopsy showed cholesterol clefts in glomeruli and small arteries in kidney. Although, it was accompanied by mild mesangial matrix accumulation, no other renal lesions that can induce acute renal failure, were
pointed out. This patient also had multiple risk factors for CCE including hypertension, diabetes mellitus and anticoagulation therapy. Clinical symptoms including concurrent ischemic changes of lower extremities were compatible for CCE. These findings strongly suggest that renal CCE which developed in renal sclerotic arteries was the cause of acute renal failure in this case. It is speculated that coronary artery bypass grafting and/or coronary angiography were the cause of renal CCE.

Although some reports have indicated the usefulness of pentoxifylline and low density lipoprotein (LDL) apheresis (1, 4), the treatment for CCE has not been established (5). Concerning the steroid therapy, a disagreement exists (6). Several reports showed that some patients with CCE benefited from low-dose corticosteroid therapy (4, 7). Hasegawa et al analyzed several cases that were treated with corticosteroid and recommended the usage of low-dose corticosteroid (0.6 mg/kg/day) (8). In the present case, the initial treatment by low-dose oral steroid seemed to have some limited effects to attenuate the progression of renal failure due to CCE, however it failed to reverse the renal failure. Interestingly, steroid pulse therapy was effective to attenuate the deterioration of renal function. This suggests that a high dose, but not a low dose, of steroid was necessary to attenuate the CCE-induced renal failure in the present case. The effectiveness of steroid pulse therapy in CCE-induced renal failure has been rarely reported before. Generally, steroid pulse therapy has not been recommended in diabetic patients, however, it is not a contraindication if careful control of blood glucose levels by insulin administration can be achieved.

Jones et al (3) divided the CCE-induced vascular changes into three phases. The early phase consists of fresh crystal emboli causing endothelial injury and early histiocytic response. The intermediate phase is characterized by a giant cell reaction and intimal proliferation. The late phase shows the encasement of the crystals by histiocytes, more intimal proliferation, and fibrous tissue formation (3). Based on this mechanism, it is speculated that steroid is effective to attenuate CCE-induced renal failure by inhibiting the inflammatory response in the early and intermediate stages of this disease.

Of note, eosinophilia seems to be associated with changes of serum creatinine. Snyder and Shapiro reported that in an animal model of CCE, panarteritis with numerous eosinophils were identified within three days after CCE occurred (9). It is also known that peripheral eosinophilia is usually transient (1). This suggests that eosinophilia might be a useful marker for the ongoing foreign body inflammatory reactions toward cholesterol crystals. Further investigation is necessary.

References

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