

Iloprost in Embolic Renal Failure

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Abstract

Cholesterol embolism is a serious disease with a high morbidity and mortality rate. There is no clear evidence that any specific treatment helps this syndrome. We report a patient who developed acute renal failure due to cholesterol crystal embolism following percutaneous transluminal angioplasty of a renal artery. Treatment with iloprost for peripheral symptoms of cholesterol emboli resulted in rapid resolution of toe cyanosis, decrease in leg pain and a significant decrease in serum creatinine shortly after initiation of treatment. One month after initiation of iloprost therapy, skin signs of cholesterol emboli disappeared and leg pain diminished. Gradually reduction in serum creatinine level was also observed (from 390 to 160 micromol/L). Eighteen months after the arteriography, the patient had stable renal function with creatinine levels of 150–160 micromol/L, and he was asymptomatic.

Key Words: Cholesterol crystal emboli, iloprost, acute renal failure.

Introduction

CHOLESTEROL CRYSTAL EMBOLISM is a multisystem disorder characterized by the occlusion of small arteries by cholesterol crystal particles which originate in ruptured atherosclerotic plaques in the aorta or, occasionally, in other large arteries (1, 2). Atheroembolism may occur spontaneously or it may occur secondary to endovascular trauma such as vascular surgery or angiographic procedures. Other etiologic factors include anticoagulation and thrombolysis. A number of patients may experience multiple triggering factors (1, 2). The proximity of the kidney to the abdominal aorta and the rich renal blood supply make the kidney a frequent target organ for atheroemboli.

Cholesterol embolism is a serious disease with a high morbidity and mortality rate. There is no clear evidence that any specific treatment helps this syndrome. We report a patient with multiple cholesterol crystal emboli in the kidneys and in the lower extremities, who had significant improvement in limb ischemia and renal function after intravenous iloprost therapy.

Case Presentation

A 52-year-old male complaining of severe headache was admitted for investigation. The patient had been suffering from hypertension for six years and was being treated with controlled-release nifedipine. He had a history of hyperlipidemia, heavy smoking and two cerebrovascular accidents, two and five years earlier. Two weeks before the current admission, the patient had complained of severe headache and was examined by the family physician. Enalapril was added to his treatment because of uncontrolled hypertension (200/100 mm Hg). On admission the patient was slightly irritable and agitated. His pulse rate was 75 beats per minute and his blood pressure was 220/110 mm Hg. He was afebrile. Fundoscopic examination revealed arteriovenous nicking and multiple, flame-shaped hemorrhages, but no papilledema. The lungs were clear. Heart sounds were regular, without murmurs. The abdomen was soft and non-tender. There was no edema of the lower extremities. The pulses were palpated on all peripheral arteries. Loud murmurs were heard over both femoral arteries and over the right renal artery. Neurological examination showed pyramidal signs consistent with an old left hemispheric stroke. The electrocardiogram showed normal sinus rhythm and voltage criteria for left ventricular hypertrophy.

The laboratory test results showed mildly impaired renal function (creatinine 110 micromol/L,

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urea 6.9 mmol/L), mild anemia (hemoglobin 11.3 mg%) and elevated blood cholesterol level (5.4 mmol/L). Potassium level was 4 mmol/L. Other laboratory tests were unremarkable.

Intravenous nitroglycerin worsened the headache without lowering the blood pressure. Intravenous hydralazine resulted in a prompt normalization of blood pressure.

Renal ultrasound demonstrated right and left kidney long axes measuring 11.5 and 10 cm, respectively. A renal technetium-DTPA flow scan showed significant reduction of perfusion of the left kidney (less than 5% normal). Uptake, concentration and excretion of isotope from the right kidney were normal. The patient underwent renal angiography, which demonstrated severe narrowing of the right renal artery. The left renal artery was totally occluded and no filling of the left kidney could be demonstrated. An initial attempt of stent insertion to the right kidney failed. Three days later a second renal angiography, under general anesthesia, was performed with successful stent insertion into the right renal artery. Angioplasty of the left renal artery was considered futile.

During the next two days the patient reported feeling well, and his kidney function was stable. On day three he started to complain of severe leg pain, and physical examination revealed livedo reticularis of both lower extremities, flank and buttocks, and scattered purple discoloration of feet and toes. The fundoscopic examination revealed no evidence of cholesterol emboli. Laboratory blood tests showed a significant deterioration of renal function with a rise in serum creatinine (220 micromol/L), and urea (6.8 mmol/L), eosinophilia (total eosinophil count 1,500 per mm³), elevated creatinine phosphokinase (1,100 units: normal 0–170 units) and myoglobin (224 ng/mL: normal 0–70 ng/mL). The blood homocysteine level was significantly elevated (29 nmol/mL: normal 0–15 nmol/mL). Screening tests for hypercoagulable state, including antiphospholipid antibodies, antithrombin III, lupus anticoagulant, activated protein C resistance and protein C and S, were within normal limits. A second renal ultrasound with Doppler showed normal blood flow to the right kidney, with no evidence of stent occlusion. Peripheral artery Doppler examination showed no hemodynamically significant arterial disease of the lower limbs, including the toes. Skin biopsy from one of the ischemic toe lesions showed cholesterol clefts. Atheroembolic renal disease due to embolization of cholesterol particles to the lower extremities and kidneys was diagnosed. During the following days, the patient remained clinically and biochemically stable. His blood pressure was

160/90 mm Hg with hydralazine, felodipine and atenolol therapy, and he was then discharged.

Two weeks later, the patient was readmitted with worsening leg pain and further deterioration of renal function. His plasma creatinine level was 390 micromol/L. Blood pressure was stable. Doppler ultrasound showed patent flow in the right renal artery. There was no improvement with intravenous fluids.

Adequate analgesic therapy with oxycodone was given. Two weeks of observation showed no improvement of renal function or lower extremity pain. The patient continued to have severe pain in his lower limbs. Based on a report of clinical improvement of cholesterol emboli with iloprost, a twenty-day course of intravenous iloprost (prosta-cyclin analogue) 25 mcg/daily was initiated (3). The treatment was then continued with 25 mcg iloprost once weekly for one year. One month after initiation of iloprost therapy, skin signs of cholesterol emboli (livedo reticularis and discoloration of the toes) disappeared and leg pain diminished. Gradually, reduction in creatinine level was also observed (from 390 to 160 micromol/L). Eighteen months after the arteriography, the patient had stable renal function with creatinine levels of 150–160 micromol/L and was asymptomatic.

Discussion

Our patient had developed acute renal failure due to cholesterol crystal embolism following percutaneous transluminal angioplasty of a renal artery. Multiple risk factors for atherosclerosis, such as male sex, hypertension, cigarette smoking, elevated homocysteine level and hyperlipidemia were present in our patient. These factors increase the risk for embolic as well as thrombotic disease.

In our patient, the classical triad of a triggering event, acute renal failure and peripheral crystal embolization (suggested by livedo reticularis and patchy purple discoloration of lower limbs associated with severe pain and cholesterol cleft on skin biopsy) supported the diagnosis of cholesterol crystal embolism syndrome. Laboratory test results also supported the diagnosis. Eosinophilia appears to be the most common extrarenal laboratory feature of cholesterol crystal embolism. Elevated creatinine phosphokinase and myoglobin levels suggested myositis secondary to emboli in our patient.

At present, there is no known treatment for the serious condition of atheromatous emboli. Thus, any therapeutic approach that might be of benefit deserves consideration. Steroid treatment is controversial. Recent reports suggest that steroid therapy might be useful for specific patients (4). In

previous studies, however, the use of corticosteroids was associated with high mortality (2).

Treatment is mostly supportive. This includes proper control of hypertension and heart failure, adequate nutrition and hydration, and support of renal function with dialysis if necessary. Surgical treatment (removal of diseased vessel wall) may be curative, but is associated with a prohibitively high mortality rate.

It is interesting to consider the possible mechanism(s) for acute renal failure in this patient. Surely the clinical presentation, including previous strokes and decreased kidney function on the left side, suggests pre-existing atherosclerotic disease. The acute changes after renal angiography are diagnostic of peripheral atheroembolic disease, and when acute renal failure occurs in this setting, it is strongly suggestive of atheroembolic renal disease. Could this be contrast-induced nephropathy? Contrast-induced nephropathy almost always occurs during the first 24–48 hours after angiography and resolves within the next few days. This patient had stable kidney function during the two first days following contrast exposure. His renal injury gradually progressed over two weeks until iloprost was started. Thus, this clinical sequence is much more consistent with atheroembolic kidney disease than with contrast-induced nephropathy.

Treatment with iloprost for peripheral symptoms of cholesterol emboli in our patient resulted in rapid resolution of toe cyanosis, improvement of leg pain and a significant decrease in serum creatinine level shortly after initiation of treatment. Iloprost, a stable prostacyclin analog with strong vasodilating and platelet antiaggregating effects, has been shown to be highly effective in treating many diseases, including peripheral vascular disease, pulmonary hypertension and Raynaud's phenomenon (5).

The effects of iloprost on renal plasma flow, renal function and the renin-angiotensin system have been studied in patients with peripheral vascular disease and normal renal function (6). This study demonstrated significantly increased renal plasma flow and fractional excretion of sodium without affecting glomerular filtration rate or plasma renin activity. Prostaglandin I₂ and its stable analog iloprost have been shown to protect the kidney in several models of experimental renal injury (7, 8).

In a series of 10 patients with systemic sclerosis and elevated resistance index of renal vessels, iloprost administration reduced the resistance index after both acute and chronic drug adminis-

tration (9). A recent report describes four cases of cholesterol emboli treated with iloprost. The main observations were improvement in distal extremity ischemia in all cases and improvement in renal function in the one patient with acute renal impairment (3). In a patient with renal artery embolism, iloprost led to improvement in renal function recovery (10).

The benefits of iloprost in pulmonary hypertension and chronic pulmonary thromboembolism, as well as in some studies of acute renal failure, certainly warrant further exploration in animals and man.

It is generally accepted that prostaglandins act as local regulators of vascular tone. They directly vasodilate afferent and efferent arterioles. In addition, prostacyclin inhibits the production of endothelin, a potent vasoconstrictor peptide. This property of iloprost may explain its effectiveness in patients with renal impairment due to renal vasospasm. However, the mechanism of action of iloprost in this patient with cholesterol embolism is unclear and needs to be investigated.

References

1. Scolari F, Tardanico R, Zani R, et al. Cholesterol crystal embolism: a recognizable cause of renal disease. *Am J Kidney Dis* 2000; 36:1089–1109.
2. Fine MJ, Kapoor W, Falanga V. Cholesterol crystal embolisation: a review of 221 cases in the English literature. *Angiology* 1987; 42:769–784.
3. Elinav E, Chajek-Shaul T, Stern M. Improvement in cholesterol emboli syndrome after iloprost therapy. *BMJ* 2002; 324(7332):268–269.
4. Belenfant X, Meyrier A, Jacquot C. Supportive treatment improves survival in multivisceral cholesterol crystal embolism. *Am J Kidney Dis* 1999; 33:840–850.
5. Fink AN, Frishman WH, Azizad M, Agarwal Y. Use of prostacyclin and its analogues in the treatment of cardiovascular disease. *Heart Dis* 1999; 1(1):29–40.
6. Angeli P, Gatta A, Caregato L, et al. Effects of iloprost, a prostacyclin analog derivate, on renal plasma flow, renal function, and renin-aldosterone system in humans. *Clin Pharmacol Ther* 1988; 44:211–216.
7. Lifschitz MD, Barnes JL. Prostaglandin I₂ attenuates ischemic acute renal failure in the rat. *Am J Physiol* 1984; 247(5 Pt 2):F714–F717.
8. Neumayer HH, Wagner K, Preuschhof L, et al. Amelioration of postschemic acute renal failure by prostacyclin analogue (iloprost): long-term studies with chronically instrumented conscious dogs. *J Cardiovasc Pharmacol* 1986; 8(4):785–790.
9. Scorza R, Rivolta R, Mascagni B, et al. Effect of iloprost infusion on resistance index of patients with systemic sclerosis. *J Rheumatol* 1997; 24:1944–1948.
10. Levin M, Nakhoul F, Keidar Z, Green J. Acute oliguric renal failure associated with unilateral renal embolism: a successful treatment with iloprost. *Am J Nephrol* 1998; 18(5):444–447.