Acute anuric renal failure with streptokinase therapy in a patient with acute venous thromboembolic disease and the review of renal side effects of streptokinase

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ÖZET

Akut venöz tromboemboli tedavisinde streptokinaz kullanımına bağlı akut anürik böbrek yetmezliği olgusu ve streptokinazın renal yan etkilerinin gözden geçirilmesi

Akut miyokard infarktüsünde, trombolitik tedavide, kullanılan streptokinazın etkileri oldukça iyi bilinmektedir. Oysa streptokinazın venöz tromboembolik hastalıkta kullanımı ile ilgili, özellikle de yan etkileriyle ilgili birçok belirsizlik bulunmaktadır. Biz metilen tetrahidrofolat redüktaz mutasyonuna ikincil derin ven trombozu ve masif pulmoner emboli gelişen bir olguda streptokinaz kullanımına bağlı, kanama olmadan veya immünolojik özellik göstermeyen akut böbrek yetmezliği tablosunu ve venöz tromboembolik hastalıkta renal yan etkileri değerlendirmek istiyoruz.

Anahtar Kelimeler: *Venöz tromboembolik hastalık, streptokinaz, böbrek yetmezliği.*

SUMMARY

Acute anuric renal failure with streptokinase therapy in a patient with acute venous thromboembolic disease and the review of renal side effects of streptokinase

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The benefits of thrombolytic therapy in acute myocardial infarction are now well established. However many uncertainties, such as adverse effects, are still remain in venous thromboembolic disease. We describe a unique patient who treated with streptokinase for the methylen tetrahydrofolate reductase mutation associated acute deep vein thrombosis and massive pulmonary embolism. After therapy patient developed acute anuric renal failure without an evidence of bleeding or immunologic reaction and we would like to review the renal side effects of streptokinase in patients with venous thromboembolic disease.

Key Words: *venous thromboembolic disease, streptokinase, renal failure.*

Streptokinase is a non-enzymatic protein of 47 kDa produced by group C beta-hemolytic streptococci (1). It is widely used as a thrombolytic agent in various thrombotic and thromboembolic disorders. The benefits of thrombolytic therapy in acute myocardial infarction are now well established. However many uncertainties, such as adverse effects, are still remain in venous thromboembolic disease (VTED) (2). The adverse effects of streptokinase can be divided into three categories: bleeding complications, reactions related to the thrombolytic property of the agent and immediate or delayed immunologic reactions (3,4). The delayed immunologic reactions to streptokinase are probably mediated by immune-complexes and the kidneys are commonly involved in such immune complex diseases (5,6). Acute anuric renal failure is a relatively rare complication following thrombolytic therapy with streptokinase for myocardial infarction (6,7). And also there are a few reports of acute renal failure complicating serum sickness-like disease following prolonged streptokinase infusion for VTED (8). However there is no reported case of acute renal impairment following streptokinase treatment for acute VTED without an allergic or immunologic reaction to streptokinase. In this report we describe an unusual patient with VTED, who developed acute anuric renal failure at the 40th hour of streptokinase infusion and later became temporary chronic failure; without immunological reaction or bleeding.

CASE REPORT

A 51-year-old woman presented with 3 days of severe dyspnea, pain on breathing and localized pain in the calf with a discrepancy in the diameter of the legs. The only relevant past history was gynecologic surgery for myoma uteri 5 years previously and there was no past history of renal or urologic disease. She was a non-smoker and was taking no regular medications. The patient told that she had not tonsillitis or a skin infection during the 6 months before her admission and she had never received streptokinase. On physical examination her blood pressure was 120/70 mmHg, heart rate was 78 beats per minute. Breath sounds were decreased and also there were crackles in the right hemithorax. Cyanosis was accompanying the distended jugular veins. Besides, “Homans’ sign” was positive in the right leg. Laboratory test results on admission included a serum hemoglobin level 12.7 g/dL, D-dimer level 3047 µg/L, and normal serum electrolytes, urea creatinine and an unremarkable urine analysis. Computed tomography (CT) angiography was performed; large intraluminal filling defects were reported both in the right and left pulmonary artery and almost in all segmental artery (Figure 1). The consolidated areas were also reported in the right lower lobe. Massive pulmonary embolism was diagnosed. Color Doppler ultrasound was performed to the lower extremities; acute thrombus was reported in all over the right calf veins. Doppler echocar-

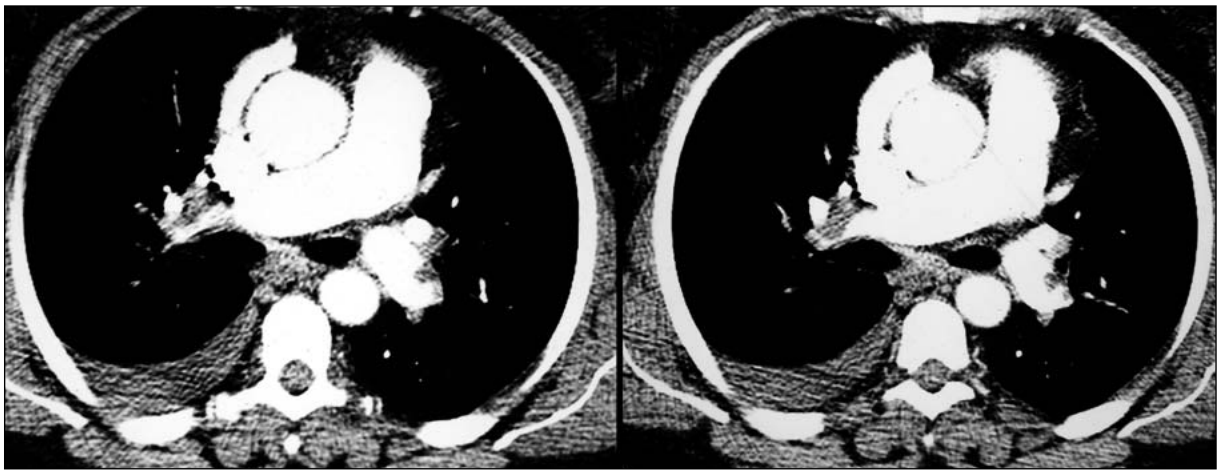

Figure 1. Computed tomography angiography; large intraluminal filling defects.

diography disclosed the presence of right ventricule (RV) dysfunction and systolic pulmonary arterial pressure was 30 mmHg. At that time; antithrombin, protein C, protein S (total and free), plasminogen and heparin cofactor-II were within reference values. Lupus anticoagulant and antiphospholipid antibodies were negative. Factor V Leiden mutation and G20210A mutation of the protrombin gene were not present. The genetic analysis of methylen tetrahydrofolate reductase (MTHFR) gene showed the patient is heterozygous for the T allele of the C677 mutation. The history and laboratory were consistent with a diagnosis of VTED and she received unfractionated heparin for one week but pulmonary embolism repeated while the therapy was effectively done during follow-up. Her blood pressure decreased to 90/60 mmHg with an increase in systolic pulmonary arterial pressure; 55 mmHg. At the same time right ventricle dysfunction was evident. We thought that, thrombolytic therapy may be a better choice than heparin to reduce mortality and she received 250.000 IU of streptokinase by IV into a peripheral vein almost half an hour. The infusion was uneventful with relief of the systemic hypotension. Intravenous infusion of 100.000 IU of streptokinase were planned for 48 hours; because the duration of thrombolytic therapy needs to be longer in deep venous thrombosis (DVT) than in pulmonary emboli. The infusion continued for 40 hours without any adverse effect however sudden oliguri were reported and the medication quited. Physical examination at the time was normal and also she was not complained about anything. There was no evidence of fever, rash, myalgia, abdominal pain, livedo reticularis or any other cutaneous eruption. After two hours she became anuric and serum creatinine and urea levels increased subsequently. Neither hematuria nor proteinuria was detected in urine analysis. Eosinophilia was not reported neither in blood nor in urine. The results of serum protein immune-electrophoresis were normal and all kinds' of immunological factors including anti-GBM antibody, ANCA, antimitocondrial antibody and ANA were negative. Also immunologic studies revealed normal ASO titer of 51.9 IU/mL (normal 0-200 IU/mL). Additionally levels of specific IgE and IgG antibodies to streptokinase were within the normal range; < 640. Serum C3, C4 levels were repeated but the results were always in normal ranges. An ultrasound and renal arterial colored Doppler ultrasound examination showed normal sized kidneys without hydronephrosis and a radionuclide renal scan did not show a perfusion defect or evidence of obstruction. Bilateral renal venous magnetic resonance imaging was also normal. There was no evidence of retroperitoneal hemorrhage. A regimen of hydration with an intravenous infusion was initiated at the oliguria stage but there was no response to intravenous challenges and high dose intravenous furasemide. Anuria persisted for three days and serum creatinine rose to 9 mg/dL despite pre-renal azotemia therapy. 10 kg weight gain was noted

and her blood pressure was 150/100 mmHg. Hemoglobin was 12.6 g/dL. The acute renal failure became chronic and the patient was placed on hemodialysis; three times a week regularly. We planned to perform renal biopsy but after two months time with hemodialysis, our patient spontaneously regained her renal functions and there was no need to the hemodialysis treatment. Serial serum creatinine levels returned to baseline within a week and the blood pressure declined to 130/85 mmHg. Follow up echocardiography reported a decrease in systolic pulmonary arterial pressure to 40 mmHg. The patient was discharged with warfarin 5 mg per once a day, the mean INR was 2.68 (target was 2.5-3.0). During a follow-up of 12 months she remained asymptomatic, without deterioration of renal functions.

DISCUSSION

To our knowledge, this is the first reported case of neither obstructive nor immunologic acute anuric renal failure after streptokinase therapy in a patient with acute venous thromboembolic disease. Clinical manifestation included acute anuric renal failure during the streptokinase infusion after 40 hours which became transient chronic failure. Consequently the patient was continued on hemodialysis for two months. Although the acute onset was brutal, our patient regained enough of her renal function two months after the onset of renal failure to make it possible to discontinue the dialysis therapy. There was no evidence of post renal obstruction or bleeding. Clinical features and immunologic studies did not demonstrate an immunological mechanism. These symptoms are non-specific and also unique. The renal failure may be related to special direct effects of the streptokinase.

The differential diagnosis of acute renal failure following thrombolytic therapy with streptokinase is presented in Table 1.

Table 1. The differential diagnosis of acute renal failure following streptokinase therapy.

Reduced renal perfusion
Hypotension or low cardiac output
Direct effect of streptokinase
Hemorrhagic shock
Related to myocardial infarction
Reperfusion induced hypotension
Obstruction of renal vasculature by emboli
Myocardial mural thrombus
Cholesterol emboli syndrome
Myoglobinuria
Immunological mechanisms
Serum sickness like syndrome
Henoch-Schonline syndrome
Cresentic glomerulonepritis
Interstitial nephritis
Proteinuria and hematuria without rise of creatinine levels
Postrenal obstruction
Retroperitoneal hemorrhage
Clots in ureters

In our patient the clinical course of pulmonary embolism was massive but she did not develop severe systemic hypotension which could have precipitated acute tubular necrosis at any time. For the patients with right ventricular dysfunction but stable hemodynamics, thrombolytic therapy may be a better choice than heparin to reduce in-hospital mortality (2,9). In DVT thrombolytic therapy is rarely used because the duration of therapy needs to be longer in DVT than in pulmonary embolism which likely increases the risk of hemorrhage, includes intracranial and fatal bleeding, with an increasing incidence among the older patients. And major bleeding is a frequent complication of streptokinase therapy may lead to hypovolemic shock and acute renal failure (10). Our patient did not have any hemorrhage. However streptokinase may cause renal insufficiency independent of hemorrhage. Conditions causing reduced renal perfusion (hypotension or low cardiac output) may induce pre renal azotemia and acute tubular necrosis. Also the hypotensive effect can lead to ischemic damage to the kidneys, especially in patients with preexisting renal disease and patients aged more than 65 years (6). Transient hypotension

at the time of streptokinase infusion is observed 10% of patients with acute myocardial infarction but there is no data in the VTED (7-9). We did not observed severe hypotension in our patient in any time.

Thrombolytic therapy may cause dislodgement of deep vein clots and may lead to increased risk of embolization. And also myocardial mural thrombus may be expected in VTED and thrombolysis, by removing mural thrombus may cause renal artery emboli. Even in patients with two functioning kidneys, unilateral embolism occasionally causes acute renal failure and oliguria (11,12). In our patient kidneys were functioning and ultrasound examination of heart and renal vascular system revealed no mural thrombosis or renal vascular system emboli.

With the frequent use of thrombolytic agents an increasing number of reported cases of renal cholesterol embolization syndrome attributed to the use of such agents has appeared. Cholesterol emboli after streptokinase infusion were described in three patients treated for venous thrombosis (13). In those patients the syndrome developed within two days of the streptokinase infusion and usually occurs after the performance of invasive vascular procedures. Physical examination reveals livedo reticularis and extensive ulcerating ecchymosis or gangrene. Systemic manifestations such as fever, myalgia, and abdominal pain are part of this syndrome and should not be confused with a hypersensitivity reaction. Eosinophilia and hypocomplementemia have been described in cholesterol emboli syndrome (14). None of them was documented in our patient.

Allergic reactions to streptokinase in humans have been reported with 18% (15). However with the increasing use of streptokinase, the frequency of both immediate and delayed hypersensitivity reactions may well increase. There are a few reports of serum sickness-like syndrome following prolonged streptokinase infusion for venous thromboembolism, although direct evidence of deposition of immune complexes in renal biopsy was not described (8). A continuous infusion may result in a more prolonged availability of circulating streptokinase, allowing time for the formation of antigen-antibody complexes in antigen excess and thus, the development of immune complex disease (1). Fever, rash, arthralgia, arthritis and hypocomplementemia are common, serum immune complexes were reported in almost of the patients. However in all of the patients symptoms resolved and serum creatinine levels decreased within 12 days (6). In our patient immunological parameters were negative and she had to continued hemodialysis, for two months; three times a week. On the other hand there are a few described patients with transient acute renal failure following repeated streptokinase therapy. Although renal biopsy was not performed, they suggested that the clinical picture was compatible with acute hypersensitivity interstitial nephritis (7). There was no acute or delayed hypersentivity reaction in our patient.

Retroperitoneal hematoma induced by streptokinase may press and obstruct the kidneys. Blood clots induced by the streptokinase therapy may also obstruct the ureters (16). Our patient had no laboratory or physical findings to suggest bleeding as a contributor to her transient reanl failure.

In conclusion, renal failure following streptokinase therapy for VTED is relatively rare complication of thrombolytic therapy. And this case demonstrates an unusual etiology of acute anuria and renal failure after intravenous administration of streptokinase. The cause may be related to special effects of the streptokinase and this case may be the preliminary case.

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