

Diffuse alveolar hemorrhages and hemorrhagic pleural effusion after thrombolytic therapy with streptokinase for acute myocardial infarction

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ABSTRACT

Thrombolytic therapy with streptokinase is commonly used in acute myocardial infarction and has markedly reduced morbidity and mortality from this condition. However, it can cause various hemorrhagic and immunological complications. We report a patient who developed diffuse pulmonary hemorrhages and bilateral hemorrhagic pleural effusion after thrombolytic therapy with streptokinase for acute myocardial infarction. This was recognized by a drop of hematocrit, pulmonary infiltrates, hemorrhagic pleural effusion and hypoxemia. The diagnosis was confirmed by demonstration of iron-laden macrophages (siderophages) in bronchoalveolar lavage. The patient required mechanical ventilation and recovered successfully. This combination of pulmonary hemorrhages and hemorrhagic pleural effusion following streptokinase therapy is extremely unusual and has not been reported previously.

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Thrombolytic therapy with streptokinase is used in the treatment of acute myocardial infarction, pulmonary embolism, recent severe deep venous thrombosis and occluded arteriovenous cannula.¹⁻⁷ However, this therapy may be associated with serious side effects. Among them bleeding is the most serious complication of thrombolytic therapy.⁸⁻¹⁰ Pulmonary hemorrhages are extremely uncommon and only few cases have been described in literature.¹¹⁻¹⁴ We describe a young male patient who developed bilateral hemorrhagic pleural effusion and diffuse alveolar hemorrhages after receiving thrombolytic therapy with streptokinase for acute myocardial infarction. To the best of our knowledge this combination of alveolar hemorrhages

and hemorrhagic pleural effusions with streptokinase therapy has not been reported previously.

Case Report. A 35-year-old male taxi driver presented to emergency room (ER) with retrosternal chest pain and sweating for the last 4 hours before presentation. He was not known diabetic or hypertensive, but had been a heavy cigarette smoker for many years. On examination he was sweaty and appeared to be in distress. His pulse was 70/minute regular and blood pressure (BP) was 60/40 mm Hg. Examination of heart, chest, abdomen and nervous system was unremarkable. His electrocardiogram

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carried out in ER was suggestive of acute inferior and right ventricular infarction. Cardiac enzymes were also significantly elevated. His hemoglobin (Hb) was 15 gm/dl, hematocrit (HCT) 43.8%, white blood cells were $19 \times 10^3/\mu\text{L}$ and platelets were $253 \times 10^3/\mu\text{L}$. Other investigations including urea, creatinine, electrolytes, liver function tests, prothrombin time (PT), partial thromboplastin time (PTT), arterial blood gases and lipid profile were within normal limits. Chest x-ray was also normal. In ER he received intravenous (IV) morphine and metoclopramide for pain relief and was started on IV fluids with normal saline. After normalization of his BP, he was given thrombolytic therapy with 1.5 MIU of streptokinase over one hour and shifted to coronary care unit for further management. After few hours the patient developed severe shortness of breath at rest. He was tachypnoeic with a respiratory rate of 30/min and had bilateral inspiratory crepitations. His oxygen saturation dropped to 90% on 4L of oxygen /minute. Chest x-ray revealed fluffy shadows in both lung fields and bilateral pleural effusions with normal cardiac size (**Figure 1**). He was initially diagnosed as having left ventricular failure and started on diuretic therapy. His condition became progressively worse and he was mechanically ventilated. An echocardiogram revealed a normal left ventricular wall motion with an ejection fraction of 73%. His central venous pressure was 12 cm H₂O and capillary wedge pressure was 15 mm Hg. Ventilation perfusion scan was of low probability for pulmonary embolism. Diagnostic pleural tapping revealed hemorrhagic aspirate. His Hb dropped to 10.5 gm/dl with HCT of 33% and platelets $170 \times 10^3 \mu\text{L}$ (**Table 1**). Serology for hepatitis B surface antigen, anti-hepatitis C virus, anti-nuclear factor and rheumatoid factors were negative. Blood, urine and sputum culture were negative. Computerized tomogram of chest showed multiple partially homogeneous opacities in both lung fields with bilateral pleural effusions (**Figure 2**). Patient was suspected with diffuse alveolar hemorrhages and hemorrhagic pleural effusions secondary to thrombolytic therapy with streptokinase.

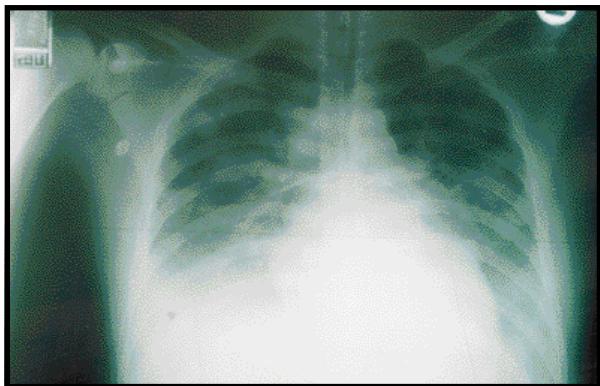


Figure 1 - Chest x-ray showing bilateral infiltrates and pleural effusions.

Table 1 - Profile of laboratory investigation during the course of illness.

Profile	On admission	Day 3	Day 10
Hemoglobin (gm/dl)	15	10.9	12
Hematocrit (%)	43.8	33	39
Platelets $\times 10^3/\mu\text{L}$	253	190	264
PT (sec)	16 (control 16 sec)	22 (control 15 sec)	16.3 (control 15 sec)
PTT(sec)	32 (control 29 sec)	66 (control 29 sec)	30 (control 31.5 sec)

sec - seconds, PT - prothrombin time, PTT - partial thromboplastin time



Figure 2 - Computerized tomogram of the chest (lung window) showing bilateral partially homogenous opacities and pleural effusions.

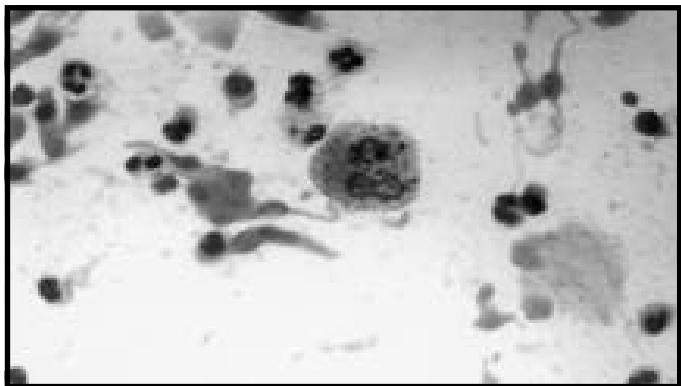


Figure 3 - Bronchoalveolar lavage showing a hemosiderin macrophage among inflammatory and epithelial cells. Hematoxylin & Eosin x 200.

He was continued on mechanical ventilation. Right intercostal tube was inserted and drained one liter of hemorrhagic fluid. Left sided pleural effusion was small in amount and did not require aspiration. Bronchoscopy was arranged and revealed normal anatomy of bronchial tree. Transbronchial biopsies showed normal histology. However, bronchoalveolar lavage (BAL) was teeming with iron laden macrophages (**Figure 3**) confirming the diagnosis of diffuse intra alveolar hemorrhages secondary to thrombolytic therapy. Bronchoalveolar lavage culture was negative. One week after admission patient's ventilatory parameters began to improve. He was weaned off from ventilator and extubated. Intercostal tube was removed. His condition remained satisfactory and was shifted to the general ward. Repeated full blood count showed a Hb of 12 gm/dl with HCT of 39% (**Table 1**). He continued to make good progress and was discharged home one week later in a stable condition.

Discussion. Thrombolytic therapy with streptokinase is recommended to be used in acute arterial thromboembolism, acute myocardial infarction, pulmonary thromboembolism, clearance of occluded arteriovenous cannula, and acute deep venous thrombosis.¹⁻⁷ However, it is most often used in the treatment of myocardial infarction either alone or followed by heparin infusion for a variable period of time.¹⁻⁴ The benefit of this therapy for improving patient's survival has proved beyond doubt in many clinical trials.^{4,15} There are many adverse effects and complications associated with streptokinase therapy. Common complications include bleeding, hypotension, fever, allergic reactions and strokes.^{8-10,16} Hemorrhage is perhaps the most serious and potentially fatal complication of this form of therapy. This is usually due to alteration of hemostatic status of patients secondary to lysis of intravascular fibrin. Common sites of bleeding include oozing from venepuncture sites, hematoma formation after intra muscular injections, ecchymosis and gingival bleeding.⁸⁻⁹ Rarely severe spontaneous bleeding can occur as intra cerebral, retroperitoneal, pericardial, genitourinary or gastrointestinal bleeding.⁸⁻¹⁰ Hemorrhagic cardiac tamponade, myocardial rupture and splenic bleeding are also reported with increasing frequency.^{17,18} In fact some recent studies have reported cerebral bleeding from thrombolysis in up to 2% of cases.¹⁹ Risk factors for hemorrhage in patients receiving thrombolytic therapy include the use of heparin or oral anticoagulants, patient's weight less than 70 kg, age over 65 year, female gender, African ancestry, use of invasive management strategies and history of hypertension and diabetes.²⁰⁻²² The risk of non-cerebral bleeding was greater after streptokinase than accelerated tissue plasminogen activator (TPA). However, the risk of intracerebral hemorrhage was greater after accelerated TPA in Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries-I trial.¹⁶ The reason for this differential effect on

cerebral verses non-cerebral bleeding is not entirely obvious. Pulmonary hemorrhagic complications are extremely unusual and only few cases of diffuse alveolar hemorrhages have been described as discovered by a Medline search.¹¹⁻¹⁴ No patient has previously been reported to have hemorrhagic pleural effusion secondary to thrombolytic therapy. Masip et al¹¹ reported a patient who developed pulmonary hemorrhages following streptokinase therapy for acute myocardial infarction. The diagnosis was made on the basis of his presentation with hemoptysis, anemia, progressive bilateral pulmonary infiltrates and severe acute respiratory failure. In another report Yigla et al¹² described a 66-year-old man who developed severe diffuse alveolar hemorrhages after streptokinase therapy for acute myocardial infarction. The diagnosis was established by his presentation with hemoptysis, anemia, hypoxemia, bilateral alveolar infiltrates and markedly increased carbon monoxide saturation capacity. Both patients recovered uneventfully after conservative treatment although one patient required mechanical ventilation for a few days. Awadh et al¹³ also described a patient who developed pulmonary hemorrhage after thrombolytic therapy for acute myocardial infarction. The diagnosis in this patient was confirmed by autopsy. Our patient was unique as he had diffuse alveolar hemorrhages as well as bilateral hemorrhagic pleural effusion secondary to thrombolytic therapy with streptokinase. The diagnosis was suspected when he failed to respond to diuretic therapy and was confirmed by a drop in HCT, marked hypoxemia requiring ventilatory support, bilateral pulmonary infiltrates, hemorrhagic pleural effusion and demonstration of siderophages in BAL after bronchoscopy. The patient was managed conservatively and required general supportive care and mechanical ventilation for a few days. He made an uneventful recovery and discharged home in a stable condition. The exact pathogenesis of this potentially fatal complication is not obvious. Some authors have proposed that an immunological reaction to a highly antigenic agent such as streptokinase may be responsible for pathogenesis.¹¹ A pre-existing pulmonary infection or presence of heart failure may be additional risk factor to predispose this complication.¹⁴ In conclusion, this is the first case report of combined alveolar hemorrhages and bilateral hemorrhagic pleural effusion secondary to thrombolytic therapy with streptokinase, and to the best of our knowledge has not been reported previously. We highlight the significance of recognition of this rare complication in patients receiving thrombolytic therapy who develop a drop of HCT, pulmonary infiltrates or unexplained hypoxemia. The patients will recover with supportive treatment, if the condition is recognized in time.

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