Spontaneous Pulmonary Hemorrhage After Thrombolytic Therapy for Acute Myocardial Infarction*

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We report a case of 63-year-old man who developed massive pulmonary hemorrhage following intravenous streptokinase for acute myocardial infarction. Pulmonary hemorrhage was diagnosed by the triad of hemoptysis, a drop in hematocrit, and a new unilateral infiltrate on chest radiograph. This diagnosis was confirmed by autopsy findings. Pulmonary hemorrhage has rarely been reported following thrombolytic therapy. We believe that pulmonary hemorrhage is a rare but a potentially life-threatening complication of thrombolytic therapy and should be considered in the differential diagnosis of pulmonary infiltrates or falling hemoglobin after thrombolytic therapy for acute myocardial infarction with no obvious site of bleeding.

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Major bleeding from the genitourinary, gastrointestinal, central nervous systems, and retroperitoneum has been reported after thrombolytic therapy for acute myocardial infarction. We report a case of spontaneous pulmonary hemorrhage following thrombolytic therapy for acute myocardial infarction and review the relevant literature. To our knowledge, this is the first case reported in the literature that was confirmed pathologically. Underlying pulmonary disease, pulmonary artery catheterization, or pulmonary edema may be predisposed to this complication.

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Case Report

A 63-year-old previously healthy man was admitted to the emergency department 45 min after the onset of severe retrosternal chest pain. He had no history of respiratory illness or a bleeding disorder. He smoked in the past but had stopped 10 years ago. His only medication was lovastatin for hypercholesterolemia.

Initial physical examination on arrival showed marked diaphoresis, blood pressure of 85/55 mm Hg, pulse rate of 56 beats/min, and respiratory rate of 20 breaths/min. His jugular venous pressure was 3 cm above the sternal angle, heart sounds were soft, and an S4 was present. His chest examination revealed bilateral inspiratory crackles in both lung bases. An electrocardiogram showed sinus bradycardia and acute anteroseptal transmural infarction. Pain was controlled with morphine and nitroglycerine. An intravenous infusion of 1.5 million units of streptokinase over 1 h followed by heparin at 1,000 U/h and a 325-mg tablet of enteric-coated aspirin were administered. Dopamine infusion at 5 µg/kg/min was started because of persistent hypotension (blood pressure of 85/60 mm Hg) lasting for 20 min.

Initial laboratory data were as follows: hemoglobin, 124 g/L; hematocrit, 38 percent; WBC count, 6.9×10⁹/L; platelet count, 203×10⁹/L; international normalized ratio, 1.2; and activated partial thromboplastin time, 30.3 s. The initial chest radiograph showed mild cardiomegaly with pulmonary vascular congestion with no other parenchymal abnormalities (Fig 1).

In the coronary care unit, he remained on a regimen of dopamine and nitroglycerine infusions, and 40 mg of furosemide intravenously was given. His mean arterial blood pressure was maintained above 75 mm Hg.

Within 45 min of starting streptokinase therapy and after several episodes of emesis, he had mild epistaxis from the right nostril that was judged to be nonsignificant, and thrombolytic therapy was continued. The activated partial thromboplastin time 12 h after streptokinase was 100 s, which confirmed a lytic state. The following day he developed cough with frank hemoptysis. A repeated chest radiograph showed a new dense opacity within the right upper lobe with inferior displacement of the minor fissure (Fig 2). Pulmonary hemorrhage was suspected and heparin and
aspirin therapy was stopped. The hemoglobin level dropped from 124 g/L to 99 g/L within 24 h and to 84 g/L within 48 h requiring transfusion of 2 U of blood. Arterial blood sample with the patient breathing 60 percent oxygen by mask showed a PaO₂ of 76 mm Hg and PCO₂ of 41 mm Hg. There was no melena stool or frank hematuria. A catheter specimen of urine was positive for blood and few red blood cells were seen per high-power field but no cellular casts. Antiglomerular basement membrane antibody was negative.

He was treated with oxygen, diuretics, and nitrates. Epistaxis stopped within 36 h of hospital admission but hemoptysis continued for 4 days. His condition gradually improved and he was discharged from the coronary care unit to the ward on the 11th hospital day. Unfortunately, he suffered a sudden cardiac arrest and died on the 12th hospital day. Postmortem examination showed bilateral pulmonary alveolar hemorrhage predominantly affecting the right upper lobe. There was no other site of hemorrhage apart from minimal submucosal hemorrhage in the bladder. Microscopic examination revealed red blood cells and hemosiderin-laden macrophages in alveolar spaces. Additional findings at autopsy were a recent pulmonary embolus to the right lower lobe and an acute transmural anteroseptal myocardial infarction with recent extension.

**DISCUSSION**

Thrombolytic therapy has been used for treatment of both acute myocardial infarction and venous thromboembolic disease for the last 30 years. Bleeding is the main adverse effect of thrombolytic therapy, usually occurring at vascular access sites. Other common sites include gastrointestinal, genitourinary, central nervous system, and retroperitoneum. We report the first case (to our knowledge) of pulmonary hemorrhage after thrombolytic therapy that was confirmed pathologically.

Pulmonary hemorrhage after thrombolytic therapy for acute myocardial infarction rarely has been reported in the literature. We did a literature search using MEDLINE (1966 to 1992) and were able to find only three case reports of pulmonary hemorrhage following thrombolytic therapy. In each case, pulmonary hemorrhage was diagnosed by the triad of hemoptysis, falling hemoglobin level or hematocrit, and new infiltrate seen on chest radiograph. Our case provides the first pathologic documentation of this complication. Minor episodes of hemoptysis were noted by Timmis and colleagues, but no major pulmonary hemorrhage was reported in their study. Disler and Rosendorff suggested that unresolved pneumonia may have been a predisposing factor to pulmonary hemorrhage in their patient. The patient described by Nathan and colleagues had a pulmonary artery wedge catheter inserted that may have contributed to the pulmonary hemorrhage. The patient described by Cueller Obispo and colleagues had recurrent ventricular fibrillation requiring electrical cardioversion and cardiopulmonary resuscitation. Our patient had no underlying respiratory disease or any invasive procedure. Potential cofactors for pulmonary hemorrhage included heart failure and pulmonary edema. Although severe heart failure and pulmonary congestion, especially secondary to mitral stenosis, may cause hemoptysis (pink frothy sputum), frank hemoptysis and asymmetric pulmonary hemorrhage are not reported with pulmonary edema alone. Increased hydrostatic pressure secondary to pulmonary venous congestion conceivably may augment alveolar hemorrhage. As our patient was receiving heparin at the time of hemorrhage, we cannot exclude a contributing effect of this medication. Reptilase time, which was not performed, would have been useful in differentiating heparin from streptokinase effect. To the best of our knowledge, however, pulmonary hemorrhage secondary to heparin therapy alone has not been reported before.

All three patients described in the literature required blood transfusions and supportive care but recovered fully from this complication. Unfortunately, our patient died suddenly and his death was probably unrelated to the pulmonary hemorrhage.

Diagnosis of pulmonary hemorrhage is usually suspected when there is hemoptysis, a fall in hemoglobin level, and new infiltrate on chest radiograph. The diagnosis can be confirmed by demonstration of hemosiderin-laden macrophages in bronchial washing or increased diffusion capacity (Dco) with pulmonary function test. We attempted to measure the diffusion capacity in our patient; however, he could not perform the Dco maneuver adequately due to his shortness of breath. In a recent report, Hsu and colleagues showed that low signal intensity of T2-weighted magnetic resonance images was diagnostic of pulmonary hemorrhage. This was thought to be secondary to the paramagnetic effect of ferric iron in the hemorrhaged blood. Although these tests are helpful in establishing the diagnosis, they are either invasive or difficult to perform in unstable patients, and clinical diagnosis remains the most important factor for such patients. Our case does fulfill the clinical criteria for pulmonary hemorrhage and this was confirmed on autopsy. Evaluation and treatment of postthrombolysis bleeding has been reviewed recently.

In summary, to our knowledge, we reported the first case
Grumolomatous Pneumonitis Following Intravesical BCG*

What Therapy Is Needed?

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A 68-year-old man developed fever, cough, and dyspnea after intravesical bacillus Calmette-Guerin (BCG). Chest radiograph revealed diffuse reticulonodular infiltrates with caseating granulomas on transbronchial biopsy specimen. Cultures were negative and the patient’s condition improved with corticosteroids. The mechanism for BCG-induced granulomatous inflammation is poorly understood. Optimal therapy includes corticosteroids. (Chest 1994; 106:1624-28)

**BCG = bacillus Calmette-Guerin; Dco = diffusing capacity of carbon monoxide**

Intravesical bacillus Calmette-Guerin (BCG) has been used in the treatment of superficial bladder cancer since 1976.1 While the incidence of local side effects such as cystitis and hematuria is high, the incidence of systemic side effects from intravesical BCG is less than 1 percent.2 In the majority of cases, systemic toxicity manifests by granulomatous inflammation involving multiple organs, which is culture negative and shows no organisms on mycobacterial stains.3 Because the pathogenesis of systemic granulomata remains unclear, treatment remains controversial. Although some cases may regress without therapy, antituberculous chemotherapy with or without corticosteroids has been used in the majority of reported cases.5 We report a case of granulomatous pneumonitis following intravesical BCG that improved slightly with no therapy, and improved markedly after corticosteroid therapy alone.

**CASE REPORT**

A 68-year-old man was diagnosed as having recurrent grade 2 transitional cell cancer of the bladder in August 1992. He was begun on a regimen of weekly intravesical BCG therapy. After the fourth BCG treatment, he noted the onset of low-grade fevers, headache, dyspnea, and cough productive of scant sputum. After the sixth BCG treatment, repeated cystoscopy with biopsy specimen showed multiple caseating granulomas with no organisms seen on special stains and negative cultures. Chest radiography revealed diffuse reticulonodular infiltrates (Fig 1). Pulmonary function tests showed mild restriction (FEV1 = 1.77 L, 73 percent predicted; FVC = 2.22 L, 74 percent predicted) with a marked decrease in diffusion (Dco = 5.71 ml/m/mm Hg, 25 percent

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**FIGURE 1.** Chest radiograph at initial presentation showing bibasilar nodular interstitial infiltrates. Chest radiograph when starting corticosteroid therapy was unchanged.