Repeated Thrombolytic Treatment for Recurrent Pulmonary Thromboembolism: A Report of 2 Cases and a Literature Review

Emine Argüder1, Ebru Parlak2, Habibe Hezer2, Ayşegül Karalezli1, H. Canan Hasanoglu1
1Department of Chest Diseases, Ankara Yıldırım Beyazıt University School of Medicine, Ankara, Turkey
2Clinic of Chest Diseases, Ankara Atatürk Training and Research Hospital, Ankara, Turkey


We present 2 cases of pulmonary thromboembolism (PTE). The first case, a 50-year-old man, was admitted to the emergency department because of sudden onset dyspnea and left side chest pain. He was diagnosed with intermediate-risk (submassive) PTE, and thrombolytic treatment was commenced. The patient fully recovered, but 5 days later, he was diagnosed with a new, high-risk PTE. The second patient, a 23-year-old woman, presented with syncope, dyspnea, and chest pain for 2 days. She was diagnosed with high-risk (massive) PTE. Thrombolytic treatment was commenced, and the patient fully recovered, too. But the later patient was also diagnosed with a new PTE 4 days later. We applied repeated thrombolytic treatment in the patients due to repeated PTE. The first patient fully recovered and was discharged from the hospital, but the second patient died because of gastrointestinal bleeding and renal insufficiency. A repeated thrombolytic treatment could be an alternative treatment for these patients, considering treatment’s risks.

KEYWORDS: Recurrent pulmonary thromboembolism, repeated thrombolytic treatment, tissue plasminogen activator

INTRODUCTION

Acute pulmonary thromboembolism (PTE) is a widespread disease with well-recognized morbidity and mortality. Patients with PTE may present with different clinical findings according to the extent of PTE. A high-risk or massive pulmonary PTE causes shock and/or constant arterial hypotension as a result of right ventricular failure. This clinical picture is obviously a life-threatening condition. Therefore, a rapid restitution of adequate pulmonary blood flow and right ventricular unloading is important to save the patient’s life. Thrombolytic therapy is recommended in the presence of hypotension or shock and without a high bleeding risk, systemically administered in the guidelines [1-3]. There is little published evidence on the repeated thrombolytic treatment of recurrent high or intermediate risk PTE. Here we reported 2 cases that developed a recurrent massive PTE, and repeated thrombolytic therapies were applied.

CASE PRESENTATIONS

Case 1

A 50-years-old man was admitted to the emergency department at our hospital due to sudden onset dyspnea and left side chest pain. Seven years before, the patient had suffered PTE and deep vein thrombosis (DVT). He had used warfarin for 3 years, and he quit it on his own. His personal history included a past PTE and chronic DVT. He had smoked 10 packs/year and had been an ex-smoker for 15 years. He had no genetic predisposition for PTE. On physical examination, the patient seemed dyspneic and tachypneic. On admission, his blood pressure was 110/70 mmHg, the pulse rate was 126 beats per minute (bpm), the respiratory rate was 24/min, and the oxygen saturation (SpO₂) of room air was 90%. A physical examination revealed significant swelling of the right leg. His laboratory findings showed elevated troponin-I (65.79 pg/mL; normal range, 0-14 pg/dL), D-dimer (>10.000 ng/mL; normal range, 0-500 ng/mL), and NT-pro brain natriuretic peptide (BNP: 978 pg/mL) levels. The arterial blood gas showed moderate hypoxia and respiratory alkalosis (pH: 7.49, pCO₂: 25.8 mmHg, pO₂: 58.2 mmHg, SaO₂: 90.8%, HCO₃: 23 mmol/L). Electrocardiography (ECG) showed sinus tachycardia at 126 bpm with S1Q3T3 pattern. A chest radiogram showed left diaphragm elevation, left upper zone infiltration, and an increased cardio-thoracic index. A computed tomography (CT) pulmonary angiogram revealed filling defects in both the pulmonary arteries, but mostly on the left with pulmonary infarction (Figure 1a-c). Filling

Address for Correspondence: Emine Argüder, Department of Chest Diseases, Ankara Yıldırım Beyazıt University School of Medicine, Ankara, Turkey
E-mail: drgullu2000@gmail.com
©Copyright 2019 by Turkish Thoracic Society - Available online at www.turkthoracj.org
defects lengthened to the lobar branches distally. Also, a CT revealed right ventricular dilatation (Figure 1d). Transthoracic echocardiogram showed increased right ventricular size and elevated pulmonary arterial (PA) pressure (60 mmHg). Vascular venous doppler of the legs showed the presence of deep vein thrombosis in the right leg. Thrombolytic therapy was planned for the patient and recombinant tissue plasminogen activator (rt-PA), alteplase infusion was commenced (100 mg/in 2 hours). An improvement in the hemodynamic status and his clinical findings were observed over the next 24 hours. Repeated 2D echocardiogram showed recovery of right ventricular overload and a decrease in in PA pressure (40 mmHg). Anticoagulation treatment low molecular weighted heparin 8,000 U was continued twice a day, and the patient was wearing a varicose stocking. On the 5th day of hospitalization, sudden onset hypotension (70/40 mmHg) and severe dyspnea developed. His SpO₂ decreased to 85%-90% despite the high-flow oxygen application with face mask. Echocardiogram was applied immediately for recurrent PTE. It showed an increased right ventricular size and falling down of the septum into the left ventricle with an increased PA pressure (110 mmHg). We decided to commence again thrombolytic therapy, and alteplase infusion was repeated (100 mg/in 2 hours). There was no major or minor bleeding during or following the thrombolytic therapy. After thrombolytic administration, the patient’s condition stabilized. The patient’s hypotension and hypoxia improved. He was stable for imaging to confirm the etiology of his presenting symptoms. A new CT pulmonary angiogram was obtained, which confirmed new defects in the right main pulmonary artery and substantially resolving on the left side (Figure 2a, b). Following the second thrombolytic application, an improvement of his symptoms and findings was observed over nearly 48 hours. A control echocardiogram showed a decreased in the PA pressure (30 mmHg). The patient made full recovery on the 2nd week, and he was discharged from the hospital 3 weeks later on lifelong warfarin. Informed consent was obtained from the patient.

**Case 2**

A 23-year-old woman presented with syncope, dyspnea, and chest pain for 2 days. She had no history of pulmonary or another disease. She was a non-smoker. There were an abortion and molar pregnancy in her medical history. Her sister had an abortion too. The patient had a pulse rate of 115 bpm, and her blood pressure was 90/60 mmHg. There were fine crackles in the right lower lobe observed on the physical exam. The systemic examination was normal. Laboratory tests showed leukocytes 14.4 K/μL (normal range 4-11 K/μL), 43.8% PMNL, platelets 189,000 K/μL (normal range 150-400 K/μL), Hb 8.1 g/dL, CRP 231 mg/L, NT-pro BNP 2,650 pg/mL, troponin 100.9 pg/mL. Renal and liver function tests were in normal range. The D-dimer level was 10,000 ng/mL (normal range 0-500 ng/mL). Transthoracic echocardiogram
revealed 65% ejection fraction, right ventricle dilatation, and 45 mmHg PA pressure. An ECG showed sinus tachycardia. There was infiltration in the right lower zone on the chest radiogram. A CT pulmonary angiogram revealed thrombus formation in both main pulmonary arteries and lobar bronchi. Parenchymal infiltration in the right lower lobe and lingula was also detected (Figure 3a, b). No thrombus was reported in the lower extremities on venous doppler ultrasound. The patient was diagnosed with high-risk PTE. An immediate medical therapy was started, and rt-PA alteplase (50 mg/in 1 hour) was given. An improvement in her hemodynamic status and her clinical findings was observed over the next 24 hours. Repeated 2D echocardiogram showed similar findings in the following 24 hours. Ceftriaxone (2 gr/day) was added to the therapy. After the alteplase therapy, subcutaneous enoxaparin (1 mg/kg) was started twice a day. On the 5th day of admission, the patient developed sudden shortness of breath. Her blood pressure was 70/50 mmHg, and oxygen saturation was 66%. Re-embolism was suspected with these findings. The patient was transferred to the intensive care unit. Alteplase (10 mg, bolus) was given and continued with 100 mg alteplase infusion for 2 hours. Cardiopulmonary arrest occurred at the same time. The patient responded to the cardiopulmonary resuscitation after 1 hour. Extracorporeal membrane oxygenation and mechanical ventilation were used. Epistaxis started after alteplase therapy. A nasogastric tube was placed. Gastrointestinal bleeding was detected, and proton pump inhibitor infusion was added to her therapy. The patient’s renal function was impaired with anuria. Uncompensated metabolic acidosis developed, and hemodialysis was needed. The laboratory abnormalities representing the severity of the disease were leukocytes 35.05 K/uL with 64.1% PMNL, thrombocytopenia (89,000 K/uL), and anemia (Hb 5.4 g/dL). The D-dimer level was 10,000 ng/mL. The INR level was too high for evaluation. Fresh frozen plasma, erythrocyte suspension, and coagulation factors were transfused for 2 days. The patient died on the 7th day upon admission. Informed consent was obtained from the patient’s father.

DISCUSSION

Acute PTE is a common disorder with an annual incidence of nearly 1 or 2 cases per 1,000 persons in general population. It is the third most common cause of cardiovascular mortality and is responsible for 100,000 to 180,000 deaths annually [4-6]. The clinical presentations of acute PTE are highly variable, ranging from pulseless electrical activity to mild

![Figure 2. a, b. In Case 1, new defects in the right main pulmonary artery and substantial resolving on the left side are seen in the computed tomography pulmonary angiogram](image)

![Figure 3. a, b. In Case 2, thrombus formation in both main pulmonary arteries and lobar bronchi are seen in the computed tomography pulmonary angiogram (a). In Case 2, parenchymal infiltration in the right lower lobe and lingula are seen in the computed tomography pulmonary angiogram (b)](image)
dyspnea [2,7]. PTE is commonly classified as high risk (massive), intermediate risk (submassive), and low risk to help determine the required treatment. Risk stratification scores are used to determine the risk of complications and associated mortality. A high-risk PTE is defined as suspected or confirmed PTE in the presence of shock, sustained hypotension, the absence of a pulse, or persistent profound bradycardia. An intermediate-risk PTE is defined as suspected or confirmed PTE with right ventricular dysfunction in the absence of shock [1,2,8]. Especially, throughout the first 3 months of PTE treatment, the ratio of recurrent PTE was 2.1%-2.8%. The risk is higher especially in cancer patients or immobilization [4,9,10].

Treatment options rely on the patient’s clinical situation and bleeding risk. For the patients who present with high-risk or massive PTE, there is consensus for prompt reperfusion treatment using systemic thrombolytic treatment [11]. Streptokinase, urokinase, and rt-PA have been approved for this indication. Thrombolytic agents convert native plasminogen to plasmin, which in turn hydrolyzes the fibrin of thromboemboli, resulting in clot lysis [12]. Thrombolytic therapy has been shown to improve the pulmonary artery pressure, arteriovenous oxygenation, pulmonary perfusion, and echocardiographic assessment, thereby relieving symptoms, preventing recurrent PE, and reducing mortality [2,13]. Also, actual studies have shown a significant role that systemic thrombolysis plays in the intermediate-risk PTE [8]. The current guidelines for PTE treatment recommend surgical embolectomy when thrombolytic treatment is contraindicated or ineffective. However, recurrent embolism and repeated thrombolytic treatment were not mentioned in this guideline [2]. Meneveau et al. [14] evaluated direction of patients with acute massive PE who do not benefit from thrombolytic treatment. They showed that surgical embolectomy provides a better course in the hospital when compared with who applied repeated thrombolytic treatment. But, in our cases, general conditions and hemodynamic parameters were not suitable for the operation. It is known that when streptokinase is insufficient, this agent cannot be given due to allergic reaction risk. But, it has been reported that rt-PA has been used in unsuccessful thrombolysis or recurrent high-risk PTE [15,16]. We chose alteplase for repeated thrombolytic therapy, because alteplase is the most common thrombolytic used for PE treatment, and it has been approved by the US Food and Drug Administration. Also, bleeding complications due to alteplase are dose dependent [17]. Absolute contraindications for thrombolytic therapy include structural intracranial disease, previous intracranial hemorrhage, ischemic stroke within 3 months, active bleeding, recent brain or spinal surgery, recent head trauma with fracture or brain injury and bleeding diathesis [8]. In our cases, there were no absolute contraindications for thrombolytic treatment.

We applied thrombolytic treatment rt-PA in the patients due to an intermediate-to-high-risk PTE at first. The patients had indications of right ventricular strain in both laboratory findings (high levels of troponin and NT-pro BNP) and ECG findings. The first patient was applied alteplase 100 mg/2 hours, while the second patient was applied alteplase 50 mg/1 hour. But, both patients recovered for clinical and laboratory findings. However, latter presentation of PTE in both patients, high-risk PTE, was seen to cause hemodynamic instability and typically a systolic blood pressure <90 mmHg. Thrombolytic treatment applied in these patients increased the mortality risk for both intermediate-to-high-risk PTE and high-risk PTE. The first case was treated successfully, while the second case died. Unfortunately, especially fast-developing hemodynamic collapse and later gastrointestinal bleeding affected the patient’s course. The limitation of our study was that there were only 2 cases. In addition, these cases demonstrate that repeated thrombolytic treatment can be effective in treating recurrent massive PTE, considering the bleeding risk.

**Informed Consent:** Written informed consents were obtained from patients and/or the relatives of the patient.

**Peer-review:** Externally peer-reviewed.


**Conflict of Interest:** The authors have no conflicts of interest to declare.

**Financial Disclosure:** The authors declared that this study has received no financial support.

**REFERENCES**


15. van den Biggelaar RJ, Slebos DJ, van der Meer J. Repeated thrombolytic therapy after initial unsuccessful thrombolysis in massive pulmonary embolism. Thorax 2008;63:89. [CrossRef]
