Successful treatment of massive pulmonary embolism in a pregnant woman, with low-dose, slow infusion of tissue plasminogen activator

Hamile bir kadında masif pulmoner embolinin düşük doz ve yavaş infüzyonla doku plazminojen aktivatörü ile başarılı tedavisi

Murat Biteker, M.D., Nilüfer Ekşi Duran, M.D., Mehmet Özkan, M.D.

Department of Cardiology, Kartal Koşuyolu Heart and Research Hospital, İstanbul

Pulmonary embolism (PE) is an important cause of morbidity and mortality during pregnancy. A 21-year-old pregnant woman presented with chest pain and progressive shortness of breath at 35 weeks of gestation. Her respiratory rate was 26 breaths/min. Electrocardiography showed sinus tachycardia and nonspecific ST-T changes. Her plasma D-dimer level was elevated (1,325 ng/ml). Transthoracic echocardiography revealed enlargement of the right ventricle and a large, highly mobile thrombus in the right atrium moving during diastole into the right ventricle. Doppler ultrasonography of the lower extremities showed bilateral acute deep femoral vein thrombosis. Following the diagnosis of right heart thrombosis with massive PE, low-dose and prolonged infusion of tissue-type plasminogen activator (25 mg in three hours) was administered. Echocardiography performed six hours after thrombolysis showed a significant decrease in the right ventricular size and complete lysis of the thrombus in the right heart. Thrombosis risk panel studies showed factor V Leiden homozygote mutation. A live newborn was delivered by cesarean section at 37 weeks of gestation. No complications were seen during a 6-month follow-up.

Key words: Pregnancy complications, cardiovascular; pulmonary embolism/drug therapy; thrombolytic therapy; tissue plasminogen activator/therapeutic use.

Pulmoner emboli (PE) hamilelik sırasında ciddi morbidite ve mortaliteye yol açan bir durumdur. Yirmi bir yaşında bir kadın, hamileliğinin 35. haftasında göğüs ağrısı ve ilerleyici nefes darlığı yakınmalarıyla başvurdu. Solunumu dakikada 26 olan hastanın elektrokardiyografisinde sinüs taşikardisi ve spesifik olmayan ST-T değişiklikleri izlendi. Plazma D-dimer düzeyi yükselmiş bulundu (1325 ng/ml). Transtorasik ekokardiyografide, sağ ventrikül genişlemesiyle birlikte, sağ atriyumda, diyastol sırasında sağ ventriküle hareket eden, büyük ve hareketli bir trombüs görüldü. Doppler ultrasonografide, her iki alt ekstremitede akut derin femoral ven trombozu izlendi. Hastaya masif PE ve sağ kalp trombozu tanısı kondu ve düşük doz, yavaş infüzyon halinde intravenöz doku plazminojen aktivatörü (3 saatte 25 mgr) uygulandı. Trombolizden altı saat sonra yapılan ekokardiyografide sağ ventrikül boyutunda belirgin düşme ve sağ kalpteki trombüsün eridiği görüldü. Trombozla ilgili risk testlerinde faktör V homozigot mutasyonu saptandı. Hastaya gebeliğin 37. haftasında sezaryenle doğum yaptırıldı ve altı aylık takibi sırasında hiçbir komplikasyonla karşılaşılmadı.

Anahtar sözcükler: Gebelik komplikasyonu, kardiyovasküler; pulmoner emboli/ilaç tedavisi; trombolitik tedavi; doku plazminojen aktivatörü/terapötik kullanım.

Pregnancy and puerperium periods are hypercoagulable states associated with increased levels of procoagulant factors (increased fibrinogen, factor V and VIII levels) and decreased anticoagulant activity (decreased protein S level and increased activated protein C resistance).[1] In pregnancy, the risk for deep vein thrombosis (DVT) and pulmonary embolism (PE) is increased five-fold compared to nonpregnant women of the same age, the latter being one of the leading causes of death during pregnancy.[2] The risk for DVT and PE in pregnancy is further increased in the presence of underlying thrombophilic disorders such as factor V Leiden mutation, prothrombin gene (G20210A) mutation, deficiencies of antithrombin, protein C, and protein S, and the

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Correspondence: Dr. Murat Biteker. Kartal Koşuyolu Yüksek İhtisas Eğitim ve Araştırma Hastanesi, Kardiyoloji Kliniği, 34846 Cevizli, İstanbul, Turkey. Tel: +90 216 - 371 50 95 e-mail: murbit2@yahoo.com

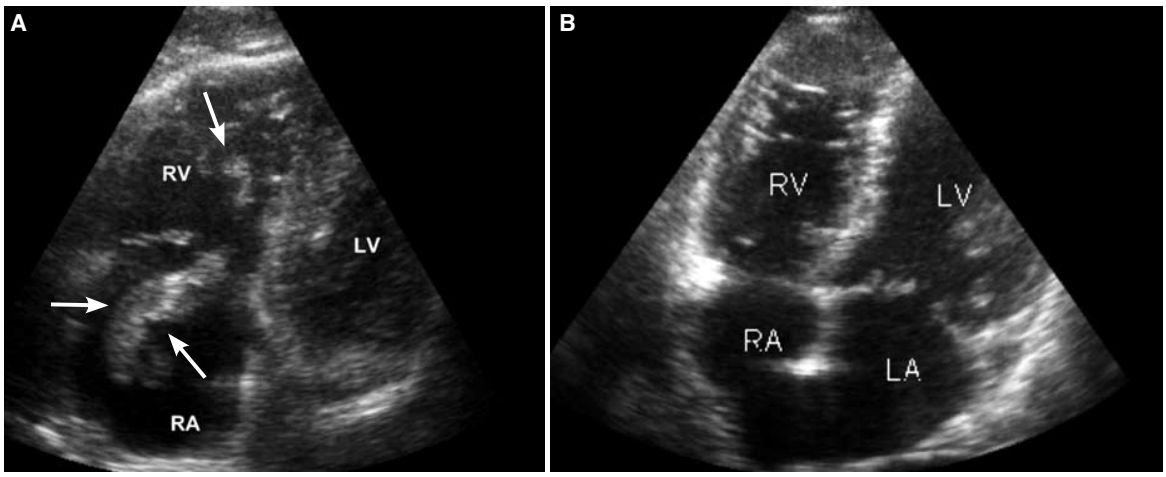

Figure 1. Transthoracic four-chamber views demonstrating **(A)** free-floating, worm-like thrombus (arrows) in the right heart, and **(B)** complete dissolution of the thrombus with normal sizes of the right ventricle and right atrium. RV: Right ventricle; LV: Left ventricle; RA: Right atrium; LA: Left atrium.

presence of antiphospholipid antibodies.[2,3] Factor V Leiden mutation is the most common genetic cause of thrombophilia, increasing the risk for DVT and PE substantially in affected women.[4] These women also have an increased risk for preeclampsia as well as miscarriage and stillbirth due to clotting in the placenta, umbilical cord, or the fetus.[2-4] Echocardiographic detection of right heart thromboemboli during PE has been reported to be 4% to 18%, showing an uncommon but life-threatening event, and representing a substantially increased risk for mortality compared to the presence of PE alone.[5]

CASE REPORT

A 21-year-old pregnant woman presented with chest pain and progressive shortness of breath of 4-day history at 35 weeks of pregnancy. On physical examination, she was mildly dyspneic and afebrile, blood pressure was 80/55 mmHg and heart rate was regular with 110 beats per minute. She had marked respiratory difficulty with a respiratory rate of 26 breaths/min and her temperature was 36.8 ºC. Her jugular veins were mildly distended and lung fields were clear. She had normal heart sounds except for a mild systolic murmur on the left lower sternal border. Oxygen saturation in room air was 93%. Electrocardiography showed sinus tachycardia and nonspecific ST-T changes. Her plasma D-dimer level was 1,325 ng/ml (normal <500 ng/ml). Transthoracic echocardiography (see supplementary video file)* revealed enlargement of the right ventricle and a large, highly mobile, worm-like thrombus in the right atrium moving during diastole into the right ventricle (Fig. 1a). Doppler examination showed moderate tricuspid regurgitation and pulmonary artery hypertension (pulmonary artery systolic pressure 45 mmHg). There was no pericardial effusion. Transesophageal echocardiography was not performed because the thrombus could be seen on the transthoracic echocardiogram. Doppler ultrasonography of the lower extremities showed bilateral acute deep femoral vein thrombosis.

The diagnosis was made as right heart thrombosis with massive PE. After evaluation of the treatment options (cardiac surgery, thrombolysis, intravenous heparin) with the patient and her family, the decision was made in favor of thrombolytic therapy (TT). We decided to administer low-dose and prolonged infusion of tissue-type plasminogen activator (t-PA) without heparin. She was given 25 mg of t-PA over three hours. The patient had an excellent response to TT. After several hours, supplemental oxygen was discontinued, the chest pain and tachycardia resolved, and her blood pressure was stabilized. She had no clinically apparent bleeding complications and no evidence for fetal compromise. Echocardiography performed six hours after thrombolysis showed a significant decrease in the right ventricular size and complete lysis of the thrombus in the right heart (Fig. 1b). After successful TT, therapeutic anticoagulation was provided with intravenous unfractionated heparin (aPTT >55 sec) until delivery. Anticardiolipin IgG and IgM and lupus anticoagulants were negative. Factor VIII and fibrinogen levels were within normal limits. There was not protein C or protein S deficiency. Thrombosis risk panel studies including factor V Leiden, factor V H1299R, prothrombin G20210A, factor XIII V34L, ß-fibrinogen-455 G-A, MTHFR A1298C, MTHFR C677T, PAI-1 4G/5G, GPIIIa L33P, ACE, ApoB R3500Q, and ApoE showed factor V

Leiden homozygote mutation. No complication was seen till 37 weeks of gestation and a live newborn was delivered by cesarean section. Afterwards, warfarin therapy was begun and titrated to achieve an international normalized ratio of 2.5-3.5. The patient was discharged in excellent condition and she was doing well during a 6-month follow-up.

DISCUSSION

Although TT is recommended as the standard, first-line treatment in patients with massive PE,[6] the optimal management of PE in pregnant patients remains unclear due to the lack of prospective trials. However, several case reports have reported success with TT in pregnant patients.[7,8] Thrombolytic therapy is especially recommended for pregnant women who are hemodynamically unstable and hypoxic. In such patients, TT should not be withheld because the patient is pregnant. Though there is no consensus on the TT protocol, usually a 2-hour infusion of 100 mg t-PA is given.[5-8] We recently reported the efficacy and safety of low-dose, prolonged t-PA infusion in an 85-year-old woman with pulmonary embolism,[9] and in patients with prosthetic valve thrombosis.[10] In this case, we decided to give low-dose, prolonged t-PA infusion until effective thrombolysis was obtained as detected by transthoracic echocardiography and the patient's clinical condition. We feel that successful outcome in a single patient may not justify this approach to be broadly used; however, low-dose and slow infusion t-PA under the guidance of transthoracic echocardiography may be a safe treatment protocol especially in pregnant patients, which needs to be validated by further studies.

**Supplementary video file associated with this article can be found in the online version.*

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