Recurrence of Idiopathic Thromboembolism During Anticoagulant Therapy

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Patients with acute pulmonary embolism and venous thromboembolism are usually treated with anticoagulant therapy for at least 3 months as the optimum duration. A patient with recurrent idiopathic venous thromboembolism at the eighth month during anticoagulation (warfarin to target international normalized ratio of 2.0–3.0) is described. The case suggests that patients with idiopathic venous thromboembolism have a high risk of recurrence, even if a strict anticoagulant regimen is followed. (Jpn Circ J 2001; 65: 755–756)

Key Words: Anticoagulation; Pulmonary embolism; Venous thromboembolism

Acute thromboembolism is usually treated with a 5–7 day course of unfractionated or low molecular weight heparin, followed by a 3-month course of oral anticoagulant therapy. However, after anticoagulant therapy is stopped, 9.5% of patients who had 6 months’ anticoagulation treatment have recurrences of venous thromboembolism over a 2-year follow-up period. A recent study suggests that the risk of recurrent venous thromboembolism is greater in patients with idiopathic venous thromboembolism than with a transient risk factor such as surgery. We describe a recurrence of venous thromboembolism at the eighth month of anticoagulant therapy in a patient with no risk factors.

Case Report

A 24-year-old woman was referred to the Kagawa Medical University Hospital because of chest pain and severe dyspnea. Two weeks before admission, she had had low-grade fever and cough with blood-streaked sputum, which was diagnosed with the common cold and she had been prescribed anti-inflammatory drugs. Her symptoms gradually worsened, and she had sudden dyspnea and was brought to the nearest hospital by ambulance 5 days before her current admission.

At the other hospital her pulse rate was regular at 150 beats/min. Blood pressure was 60/30 mmHg and her respiratory rate was 40 breaths/min. Arterial blood gases (breathing room air) showed a PaO2 of 47.6 mmHg and PaCO2 of 29.3 mmHg. Cardiac examination revealed a normal first heart sound and an accentuated pulmonic component of the second heart sound. Chest radiography showed a mild cardiomegaly (cardiothoracic ratio, 55%), and an electrocardiogram showed an T wave inversion in leads II, III and aVf. An echocardiogram showed right ventricular dilatation and abnormal interventricular septal wall motion (Fig 1). Systolic wave and T wave inversion in leads II, III and aVf. An echocardiogram showed right ventricular dilatation and abnormal interventricular septal wall motion (Fig 1). Systolic wave and T wave inversion in leads II, III and aVf. An echocardiogram showed right ventricular dilatation and abnormal interventricular septal wall motion (Fig 1).

Fig 1. Echocardiogram of the parasternal short-axis view. The right ventricle (RV) is enlarged and the interventricular septum is shifted toward the left ventricle (LV).

Fig 2. Spiral computed tomography of the lung showing thrombi in the right main pulmonary artery and descending branch of the left pulmonary artery (arrows).
pulmonary arterial pressure, which was calculated as \(4 \times \) (velocity of tricuspid regurgitation); was 70 mmHg. Spiral computed tomography revealed multiple thromboemboli (Fig 2). The patient was transferred to Kagawa Medical University Hospital for pulmonary angiography and thromboembolectomy.

Venous ultrasonography showed a movable left femoral vein thrombus. A \(^{99m}\)Tc macro aggregated albumin lung scan revealed multiple defects in both lungs, and pulmonary angiography also showed multiple pulmonary emboli. The pulmonary artery pressure, which was measured using a Swan – Ganz catheter, was 38/22 mmHg with a mean value of 29 mmHg. The tip of the Swan – Ganz catheter was positioned in the right pulmonary artery, and tissue plasminogen activator (monteplase 1.6 million U/day) was given through the side hole of the catheter in the right atrium. The patient improved, with arterial blood gases showing a PaO2 of 149.0 mmHg and a PaCO2 of 37.0 mmHg (breathing 100% O2 at a flow of 5 L/min through a mask). A temporary vena cava filter was placed in the inferior vena cava to prevent further pulmonary thromboembolism. For thrombolysis, tissue plasminogen activator (monteplase 1.6 million U/day) was administered for 3 days, and heparin (4×104 U/day) was administered continuously. Venography revealed resolution of the embolus. Oral anticoagulation with warfarin sodium was started on the 10th day of admission, targeted to an international normalized ratio (INR) of 2.0–3.0.

Although thrombophilia was observed, the patient did not have a family history of thrombophilia, and the levels of antithrombin III (93%; normal range, 80–120%) and protein C (102%; normal range, 73–142%) were within normal range; however, the level of protein S (86 mg/ml; normal range, 4.0–13.8 mg/ml) was higher. Anti-phospholipid syndrome were not detected (anti-CL-\(\beta\)-2GP1 antibody of 1.7 U/ml; normal range, <3.5 U/ml). The laboratory data, including a platelet count of 32.4×10\(^4\) were all within normal limits after treatment of the pulmonary embolism.

Eight months later, the patient was admitted because of pain and swelling in her left leg despite anticoagulant therapy. Enhanced computed tomography showed a thrombus in the left femoral vein (Fig 3). The INR was 3.74 at the time of admission. Treatment with intravenous drip infusion of heparin (2×10\(^4\) U/day) for 1 week improved the pain and swelling in her left leg and venography 1 month later revealed no sign of embolus in the bilateral femoral vein or inferior vena cava.

**Discussion**

In 1960, Barritt and Jordan\(^6\) showed that anticoagulation therapy reduces mortality in patients with pulmonary thromboembolism. Initial therapy with intravenous heparin is followed by oral anticoagulation with warfarin. Although the Research Committee of the British Thoracic Society\(^3\) and Kearon et al\(^7\) both recommend that patients without persistent underlying causes or risk factors should receive anticoagulant for 3 months, the optimal duration of oral anticoagulant therapy is still a matter of debate.

Schulman et al compared the recurrence rate of venous thromboembolism for 6 weeks and 6 months of oral anticoagulant treatment. They found that although 6 months of oral anticoagulation treatment after a first episode of venous thromboembolism leads to a lower recurrence rate than the 6-week treatment regimen, this difference occurred between 6 weeks and 6 months after the initiation of treatment. Consequently, the rates of recurrence were nearly identical after anticoagulation therapy was completed. Furthermore, in 454 patients (permanent or unknown risk factor patients, 287) of a 6-month treatment group with a target INR of 2.0–2.85, a cumulative probability of recurrence was 0.01 (6 cases) during treatment even if anticoagulant therapy was strictly followed. In the present case, we administered continuous oral anticoagulation therapy after the first episode of pulmonary thromboembolism, and deep venous thromboembolism recurred at the eighth month of treatment (INR, 2.0–3.0).

With regard to the recurrence of venous thromboembolism after deep vein thrombus, Hansson et al reported that the 1-year or 5-year cumulative incidence of its recurrence was 7.0% or 21.5%, respectively, after the first event. Heit et al followed up 404 patients with deep vein thrombosis and pulmonary embolism for 10 years and reported that venous thromboembolism recurs particularly within the first 6–12 months (cumulative recurrence at 12 months, 12.9%) and continues to recur for at least 10 years (cumulative recurrence at 5 years, 22.8%; at 10 years, 30.4%). Consequently, the present case suggests that patients with deep venous thromboembolism should be treated with anticoagulant agents for at least 12 months and carefully observed even when anticoagulation treatment is strictly followed.

**References**