Thrombectomy and Catheter-Directed Thrombolysis Combined With Antithrombin Concentrate for Treatment of Antithrombin Deficiency Complicated by Acute Deep Vein Thrombosis That Is Refractory to Anticoagulation

A Case Report

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Summary

A 22-year-old male was admitted to our hospital with deep vein thrombosis that was complicated by antithrombin deficiency. This deficiency was refractory to anticoagulation therapy. Although catheter-directed thrombolysis could not reperfuse the total occlusion in the left deep vein, a combination of thrombectomy, catheter-directed thrombolysis, and antithrombin concentrate treatment was able to dissolve the clots and ameliorate the blood flow into the left deep vein. Antithrombin concentrate administration would be effective in the treatment of antithrombin deficiency with medical refractory deep vein thrombosis. (Int Heart J 2016; 57: 649-653)

Key words: Medical refractory DVT, Antithrombin concentrate

Antithrombin deficiency is an inherited thrombophilia with a genetic tendency to cause venous thromboembolism.1,2) Deep vein thrombosis is a frequent serious complication in patients with antithrombin deficiency.2,3) We report here a case of antithrombin deficiency that was complicated by acute deep vein thrombosis and refractory to anticoagulation. The patient was successfully treated by thrombectomy and catheter-directed thrombolysis (CDT) combined with antithrombin concentrate.

Case Report

In June 2012, a 22-year-old male with syncope while walking was admitted to our department. He had been sitting in a chair for a long time to study for his school examinations. He had no past medical history and no past history of limb swelling. He was a smoker. His grandmother had a past history of pulmonary embolism. He was conscious on admission. Physical examination showed swelling of the left lower limb. His heart rate was 141 beats/min and regular, and his arterial blood pressure was 139/87 mmHg. Auscultation of the lungs and heart revealed no inspiratory rales. A 12-lead electrocardiogram showed S waves in lead I, and flat T waves in III and aVF. Echocardiography demonstrated a dilated and hypokinet ic right ventricle (RV) with moderate tricuspid regurgitation. The maximum tricuspid regurgitation velocity was 3.5 m/s indicating pulmonary hypertension. A conventional chest CT was performed. A CT image at the pulmonary artery level with intravenous contrast revealed thrombus in the bilateral pulmonary (Figure 1) arteries and the left lower limb (Figure 2). Pulmonary perfusion scanning showed scattered defects in the bilateral pulmonary perfusion (Figure 3), and lower limb perfusion scanning showed severe perfusion defect and development of collateral circulation (Figure 4).

The patient was diagnosed with acute pulmonary artery thromboembolism (PTE) due to acute deep vein thrombosis (DVT). The plasma levels of protein C and protein S activities were within normal limits. Lupus anticoagulant and anticardiolipin antibody were not detected. Conventionally, we had the patient put on an elastic stocking on admission to mitigate the pain and edema of the left lower limb. Conventional anticoagulant treatment using heparin and oral anticoagulation were indicated, and an intravenous filter was initiated on admission. Heparin was continued with the dose adjusted to maintain an effective activated partial thromboplastin time (APTT) of 46-83 seconds until an international normalized ratio of 2.0-3.0 was maintained with warfarin sodium.

On the 4th day of hospitalization, echocardiography revealed a normalized RV with trivial tricuspid regurgitation, indicating that estimated RV pressure was 31 mmHg. However, the swelling of the left lower limb had progressed, and CT scanning with intravenous contrast showed increased thrombus in the lower left limb on the 7th day of hospitalization. He received continuous infusion of urokinase (240,000 U/day) for 8 days from the 11th day of hospitalization, but the swelling did
not cease. Color Doppler ultrasonography revealed a residual massive thrombus filling the lumen of the popliteal, femoral, and external iliac veins. On the 19th day of hospitalization, a 9Fr peripheral guide catheter using a Vista Bright Tip (Johnson & Johnson Co., Ltd., NY, USA) was introduced into the right femoral vein. Manual thrombus aspiration was performed, but failed to remove the thrombus from the left popliteal vein to the left iliac vein because of a large amount of newly constant thrombus formation. CDT was performed using a Fountain Infusion System (Merit Medical Systems, Inc. UT, USA). The

Figure 1. Thrombus was detected in the bilateral pulmonary artery by CT scanning with intravenous contrast.

Figure 2. Thrombus was detected in the left lower limb by CT scanning with intravenous contrast.

Figure 3. Segmental perfusion defect was documented in the bilateral upper lobes and the left lower lobe. Scattered defects in the bilateral pulmonary perfusion indicated acute pulmonary thromboembolism.
4Fr Fountain catheter was introduced into the left iliac vein, and urokinase (240,000 U) was infused intravenously. Subsequently, continuous infusion of urokinase (240,000 U/day) via the Fountain catheter was performed for 9 days.

On admission, while antithrombin antigen was not calculated, it was 47% on the 7th day of hospitalization, indicating antithrombin deficiency. Therefore, after the infusion of antithrombin concentrate (1500 U/day) for 2 days, thrombectomy and CDT were performed on the 30th day. A 8Fr peripheral guide catheter using a Vista Bright Tip (Johnson & Johnson)
was introduced into the left popliteal vein. Manual thrombus aspiration was performed, which successfully removed the thrombus in the left popliteal vein without newly constant thrombus formation (Figure 5). Subsequently, the Fountain catheter was introduced into the left iliac vein, and urokinase (240,000 U) was infused via the Fountain catheter.

Additional balloon angioplasty was performed using 5 Fr PowerFlex PTA (Johnson & Johnson). Balloon angioplasty improved the blood flow around the upper side of the left knee (Figure 6), and swelling and pain of the left limb were alleviated (Figure 7). Antithrombin antigen was 47% at the time of hospital discharge, and warfarin sodium was continued after leaving the hospital. The intravenous filter was removed prior to discharge. At 24 months after discharge, he exhibited no recurrence of swelling and pain of the left limb. Moreover, antithrombin antigen remained low, indicating inherited antithrombin deficiency rather than acquired antithrombin deficiency. No genetic testing was done.

**Discussion**

The normal range of antithrombin varies between 75 and 120 percent. Patients with antithrombin deficiency usually range from 40 to 60 percent. It has been reported that acquired antithrombin deficiency does not contribute to increased thrombosis. No previous report has documented the efficacy of antithrombin concentrate for treating patients with acquired antithrombin deficiency.\(^3,4\) Therefore, regarding the use of antithrombin concentrate, we should accurately diagnose inherited or acquired antithrombin deficiency, because acute thrombosis by itself can transiently reduce antithrombin levels.\(^3\) However, we administered antithrombin concentrate in the present case, although we could not make a definite diagnosis of inherited or acquired antithrombin deficiency. In this regard, we cannot assert that the use of antithrombin concentrate was completely appropriate in the present case.

Because PTS is reportedly associated with reduced quality of life,\(^5\) we concluded that complete removal of the venous thrombus in the acute phase would be necessary. Therefore, we performed thrombectomy and CDT combined with antithrombin concentrate as a pretreatment without evidence of the efficacy.

The efficacy of our strategy was demonstrated by the fact that antithrombin concentrate enabled a large amount of thrombus to be removed. Thrombectomy and CDT without antithrombin concentrate resulted in incomplete reperfusion because of constant formation of new clots in the left lower limb. Conversely, thrombectomy and CDT combined with antithrombin concentrate prevented the clot formation, leading to complete reperfusion after the balloon angioplasty.

Consequently, we believe that the patient had inherited antithrombin deficiency. At first, DVT complicating acute PTE occurred in the young male patient with a family history of acute pulmonary embolism and without inducible risk factors for thrombosis. Next, combined therapy with antithrombin concentrate was very effective. Finally, antithrombin antigen remained at a low level at 6 months after the discharge when there should be no influence of acute thrombosis or anticoagulant therapy on the concentrations of antithrombin antigen.

In multiple reports, antithrombin concentrate has been given collectively with heparin, although a conventional strategy for patients with inherited antithrombin deficiency who suffered from DVT has not been established.\(^3,4,8,9\) However, thrombectomy and CDT combined with antithrombin concentrate has not been reported in patients with antithrombin deficiency. To the best of our knowledge, this is the first report suggesting the efficacy of thrombectomy and CDT combined with antithrombin concentrate to treat antithrombin deficiency that was complicated by acute deep vein thrombosis and refractory to anticoagulation. He exhibited no recurrence of PTE. Temporary intravenous filter placement may also play a key role in the prevention of PTE in patients with medical refractory DVT.\(^10\) On the other hand, it has been reported that the incidence of bleeding complications does not depend on thrombosis location.\(^11\) Fortunately, he exhibited no incidence of bleeding complications irrespective of the intensive therapy to
remove the thrombus in the left lower limb. Consequently, we believe that our strategy was most suitable for this patient with medical refractory DVT.

We initiated anticoagulation therapy with the dose adjusted to maintain effective APTT, and we asked the patient to put on an elastic stoking stocking on admission. We do not know precisely why the DVT had been aggravated, although the time of bed rest might have been too long after admission.

In conclusion, thrombectomy and CDT combined with antithrombin concentrate is an appropriate approach to treat thrombosis that is refractory to conventional anticoagulation in patients with antithrombin deficiency.

DISCLOSURES

The authors have no conflicts of interest to disclose.

REFERENCES