Case Studies

Warfarin-Resistant Deep Vein Thrombosis during the Treatment of Acute Ischemic Stroke in Lung Adenocarcinoma

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Case Report: A 66-year-old man with acute ischemic stroke in the setting of lung adenocarcinoma developed acute-onset deep vein thrombosis (DVT) of the lower limbs after changing to warfarin from a heparin combination. The diagnosis of warfarin-resistant DVT was established based on the laboratory data and clinical evaluation. Heparin administration resulted in good control of thrombin regulation. Cancer patients are at high risk of venous thromboembolism, and the combination of these 2 conditions is known as Trousseau's syndrome. *Conclusion:* Our report suggests that heparin administration may provide good control of thromboembolic events, although there is no established medical treatment to extend the survival of patients with Trousseau's syndrome. **Key Words:** Acute ischemic stroke—deep venous thrombosis—Trousseau's syndrome—lung cancer—warfarin—heparin.

Introduction

Venous thromboembolism (VTE) is one of the most common complications in cancer patients and is strongly associated with lung cancer.[1,2] The complication of thromboembolism with malignant tumors is known as Trousseau's syndrome. Various clinical conditions coexisting with cancer have been labeled Trousseau's syndrome, ranging from ischemic stroke to any type of coagulopathy.[3] The pathological mechanism of Trousseau's syndrome remains unknown, and the evidence for medical treatment has not been established. Although patients with deep vein thrombosis (DVT) are usually treated with heparin followed by oral anticoagulants, such as warfarin, some patients with malignancy not only show resistance to warfarin but also develop DVT even under warfarin treatment. Here we present a case report of a lung cancer patient who developed warfarin-resistant DVT during the treatment of acute ischemic stroke. We report

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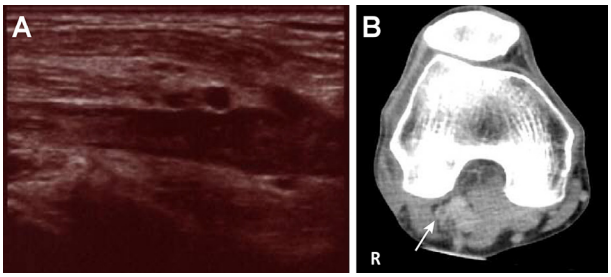

Figure 1. *Ultrasound (A) and contrast-enhanced computed tomography (B) images of the lower extremities reveal the presence of thrombi (arrow) in the right popliteal vein 2 weeks before hospitalization. Abbreviation: R, right.*

that it might be beneficial to elucidate the clinical features and the condition of the warfarin-resistant DVT in cancer patients.

Case Report

A 66-year-old man was referred to our hospital for acute-onset dysphagia and left-hand clumsiness. Ten years prior, the patient had been treated for diabetes with an oral hypoglycemic agent. Three years prior, the patient was diagnosed with lung cancer with bone metastases (stage IV) associated with back pain and was prescribed gefitinib after bronchoscopic biopsy. Two years prior, the lung cancer was pathologically diagnosed as adenocarcinoma and surgical resection of the lung tumor was performed. Two months before hospitalization the patient could maintain his activities of daily living, but the serum concentrations of the tumor markers carcinoembryonic antigen (5.5 ng/mL) and cytokeratin-19 fragments (4.2 ng/mL) were elevated. At that time, the patient also presented with muscle pain in both legs. Edoxaban (60 mg daily) was started because the patient was diagnosed with DVT based on the elevation of the D-dimer level (10.2 μg/mL), the ultrasound examination of the lower extremities, and the contrast-enhanced computed tomography that showed thrombi in his right popliteal vein 2 weeks before hospitalization (Fig 1). The presence of bone metastases was newly detected by contrast-enhanced computed tomography at that time as well. On admission, the patient's neurological examination revealed mild left facial paralysis, dysarthria, and left-hand clumsiness, indicating a National Institutes of Health Stroke Scale score of 3. Brain magnetic resonance imaging showed multiple acute infarctions in the right occipital lobe and the bilateral anterior lobe, the parietal lobe, and the cerebellar hemisphere (Fig 2, A-C). Magnetic resonance angiography showed no evidence of stenosis or occlusion of the intracranial arteries (Fig 2, D). The laboratory data on admission showed high levels of D-dimer (8.8 μg/mL) and soluble fibrin monomer complex (>150 μg/mL), indicating a hypercoagulable state. The patient's serum liver and kidney function, electrolytes, and lipid were within normal limits, and his hemoglobin A1c concentration was 5.8%. The patient had a slightly low antithrombin III level (77%), had no deficiency of protein C (83%) or protein S (124%), and was negative for lupus anticoagulant and anticardiolipin antibodies. All other known causes of stroke were ruled out by additional investigations, including carotid artery ultrasonography, transthoracic echocardiography, transesophageal echocardiography, and Holter electrocardiography. Thus, we diagnosed an undetermined cerebral infarction based on the Trial of Org 10172 in Acute Stroke Treatment.[4] Because the multiple bilateral infarctions strongly suggested a diagnosis of embolic infarction, we selected anticoagulation therapy. The patient was started on warfarin (2 mg daily) with heparin because the ischemic stroke had occurred under edoxaban administration. The clinical course of ischemic stroke was good, and the patient improved with only a slight dysarthria after rehabilitation. Brain magnetic resonance imaging conducted on day 30 showed no new infarction. We increased the dose of warfarin to an INR of 2-3, and discontinued heparin when warfarin reached 4.5 mg daily (international normalized ratio [INR] 1.98, D-dimer level 1.7 μg/mL) on day 26. Two days after interrupting heparin, the patient presented with muscle pain in the left leg. The next day, the patient's D-dimer level increased to 22.1 μg/mL, and the ultrasound of his lower extremities revealed new thrombi in the left popliteal–soleal vein. When we restarted heparin administration and increased the dose of warfarin (6 mg daily), the INR increased to 2.49, the thrombin–antithrombin (TAT) complex (1.6 ng/mL), protein

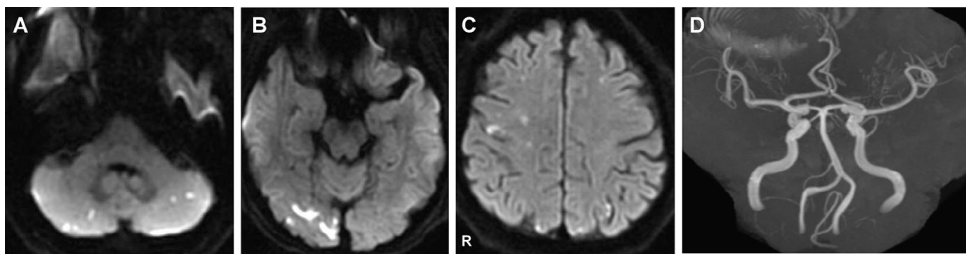

Figure 2. *Brain magnetic resonance image on admission. Diffusion-weighted image shows hyperintense lesions, indicating an acute infarction in the right occipital lobe and the bilateral anterior lobe, the parietal lobe, and the cerebellar hemisphere (A-C). Magnetic resonance angiography showed no evidence of stenosis or occlusion of the carotid or intracranial arteries (D). Abbreviation: R, right.*