Journal of Cardiology Cases 8 (2013) e77–e80

Contents lists available at www.sciencedirect.com

Journal of Cardiology Cases

journal homepage: www.elsevier.com/locate/jccase

Case Report

Dramatic response to low-dose rivaroxaban in an Asian patient with deep vein thrombosis and pulmonary embolism

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ARTICLE INFO

Article history:
Received 4 February 2013
Received in revised form 24 March 2013
Accepted 8 May 2013

Keywords:
Deep vein
Thrombosis
Pulmonary embolism
Rivaroxaban
Warfarin

ABSTRACT

We report a case of deep venous thrombosis and pulmonary embolism treated with rivaroxaban due to warfarin allergy. The patient responded well to a low dose of 15 mg/day. There has been a report about treating patients with atrial fibrillation using a low dose of rivaroxaban in Japan, but no previous reports about deep vein thrombosis/pulmonary embolism. This case suggests that rivaroxaban could be an alternative to warfarin for the treatment of deep vein thrombosis and pulmonary embolism in Japanese patients with warfarin allergy.

<**Learning objective:** Recently, several new anticoagulant medications have been released, but their efficacy has not been clarified. Rivaroxaban has shown efficacy for atrial fibrillation, deep vein thrombosis, and pulmonary embolism in Europe and the USA, but this has not been demonstrated in Japan. The present case suggests that rivaroxaban can improve deep vein thrombosis and pulmonary embolism in Japanese patients at a low dose.>

Introduction

Currently, warfarin is the most common medication employed for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) after acute treatment with intravenous heparin and there have been many reports that strongly support its efficacy [1–3]. Although several other oral anticoagulants have been released, their efficacy remains less certain. We experienced dramatic improvement of DVT and PE in a patient who was allergic to warfarin, after treatment with rivaroxaban, an anticoagulant that is not approved for these conditions in Japan.

Case report

A 41-year-old Korean man was referred to our hospital with shortness of breath and pain in his right leg. The patient had developed these symptoms one week earlier and they had become more severe over time. His medical history and family history did not appear to be contributory and his only medication was an antidepressant agent that he had been taking for two years. The patient had a history of smoking 10 cigarettes a day from 20 to 35 years old.

Physical examination showed that his right lower limb was swollen and reddened. Neurological examination revealed intact cranial nerves, with preservation of comprehension and speech. Muscle power was normal in all extremities and his deep tendon reflexes were normal. The electrocardiogram showed sinus rhythm (58 beats/min) with right ventricular conduction delay in leads V1–V2. Elevation of D-dimer (7.2 μg/dl) and C-reactive protein (10.74 mg/dl) was detected by laboratory tests.

Contrast-enhanced computed tomography detected both DVT in the right lower limb and PE (Fig. 1). There was diffuse thrombus in the right common iliac vein, extending into the inferior vena cava (IVC). There was also thrombus in the upper and lower branches of the right main pulmonary artery.

The patient was treated by placement of an IVC filter, followed by intravenous administration of monteplase (1,600,000 units) and heparin (15,000 units/day), as well as oral warfarin (3.75–4.00 mg/day).

Doppler ultrasound of the lower extremities was done after placement of the IVC filter and revealed complete obstruction below the superficial femoral vein, with mural thrombosis above the common femoral vein.

We adjusted the dose of warfarin by monitoring the prothrombin time (international normalized ratio: INR), aiming for a range between 2.0 and 3.0. The INR was controlled at 2.07–2.73. However, repeat Doppler ultrasound, which was performed several times to follow his progress, showed no improvement in the thrombosis.

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http://dx.doi.org/10.1016/j.jccase.2013.05.002

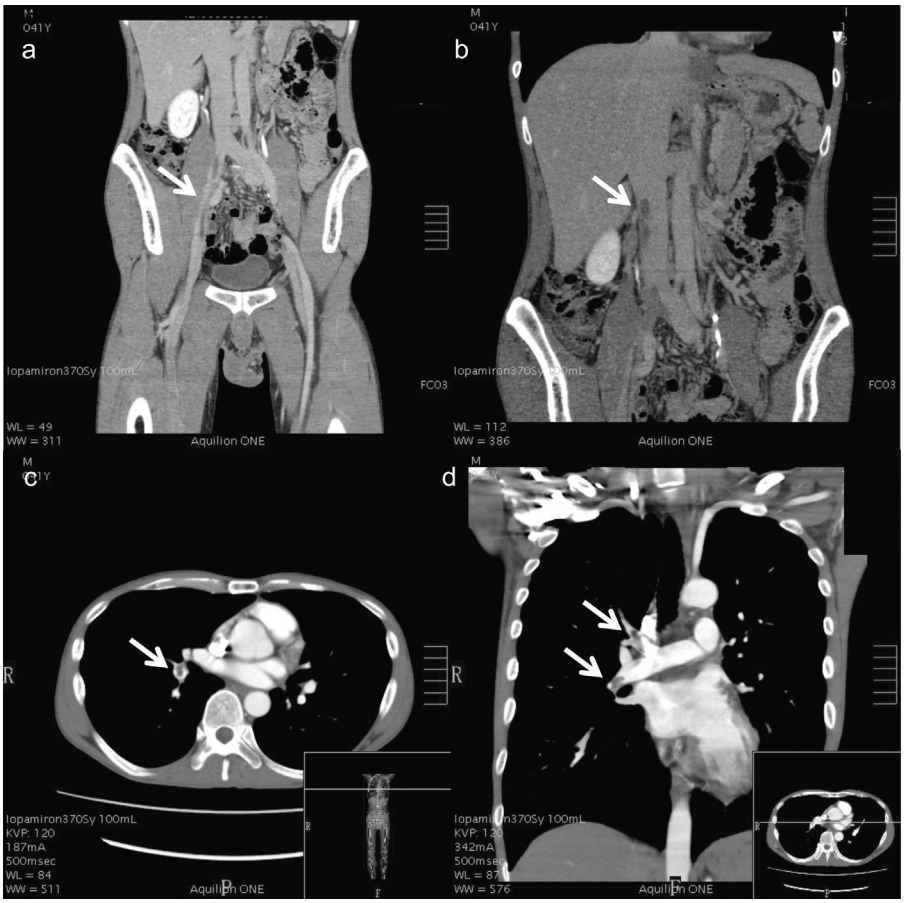

Fig. 1. Contrast enhanced computed tomography. (a) Thrombus in the right common iliac vein (coronal section). (b) Thrombus extending into the inferior vena cava (coronal section). (c and d) Thrombus in the branches of the right main pulmonary artery (horizontal section).

At 16 days after admission, we tried to remove the IVC filter, but massive thrombi were detected. Therefore, removal of thrombi by suction using the guiding sheath was performed, after which the IVC filter was taken out and then replaced in the IVC.

On day 11 of treatment with heparin and warfarin, he developed widespread erythematous papules that covered him from head to foot. He also complained of itching. Because a drug eruption was considered possible, the drug-induced lymphocyte stimulation test was done for each of the suspected medications and it was positive for warfarin. Accordingly, treatment with warfarin was stopped and rivaroxaban (15 mg/day) was administered instead. Subsequently, his rash resolved slowly and the pain in his right lower limb subsided. Activated partial thromboplastin time was controlled at 31.6–59.4 in the setting of rivaroxaban.

Protein C and antithrombin III levels were low at the time of admission, but measurement of protein C, protein S, and antithrombin III is unreliable in the setting of an acute thromboembolic event. His coagulation work-up showed no evidence of a plasminogen abnormality, antiphospholipid antibody syndrome, systemic lupus erythematosus, or other connective tissue diseases.

After checking that it was satisfactory by exercise tolerance test, the patient was discharged 31 days after admission, following improvement of the pain and swelling in his right lower limb. In addition, the laboratory tests showed the lowering of D-dimer (1.0 μg/dl) and C-reactive protein (0.03 mg/dl).

Two months after discharge, contrast-enhanced computed tomography was repeated to evaluate his progress. This showed that almost all thrombus had been cleared from the femoral vein and the pulmonary artery, with only slight residual thrombus in the superficial femoral vein (Fig. 2). The patient had no major or minor bleeding complications while on anticoagulant therapy.

Discussion

Intravenous monteplase and heparin with oral warfarin are the standard treatment for DVT and PE. Maintaining the INR in the range of 2.0–3.0 is recommended from the results of a study comparing low-intensity warfarin therapy (INR = 1.5–1.9) with conventional therapy (INR = 2.0–3.0) [4], and a study comparing high-intensity therapy (INR = 3.0–4.5) with conventional therapy [5].

The reason why warfarin was not effective for DVT and PE was not apparent in this patient. Heparin-induced thrombocytopenia was not complicated, for the number of platelets was not decreased in the setting of heparin. PT-INR was controlled at 2.07–2.73, effective control for DVT and PE. However, there was a possibility that the duration at the effective blood concentration of warfarin was not sufficient. Although PT-INR value was 2.07–2.73 at that time, warfarin was continued for only about 17 days because of the allergy.

In the present case, we had to abandon the use of warfarin because of allergy, so we selected rivaroxaban as a substitute. We chose rivaroxaban because it has demonstrated non-inferiority to warfarin for the treatment of DVT and PE [6–8], and because it is reported to show higher efficacy than enoxaparin with no difference in safety [9].

Although rivaroxaban has not been approved for the treatment of DVT and PE in Japan, the US Food and Drug Administration (FDA)