INTERNAL MEDICINE

□ CASE REPORT □

Rivaroxaban Therapy Resulting in the Resolution of Right Atrial Thrombosis Resistant to Ordinary Control with Warfarin in a Patient with Atrial Fibrillation

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Abstract

A 72-year-old man with non-valvular atrial fibrillation and metastatic liver and lung cancer after surgery for colon cancer developed thrombosis in the right atrium one month after decreasing the dose of warfarin due to the introduction of double anti-platelet therapy for coronary stent implantation. Restoring the warfarin dose with ordinary control for two months did not result in any changes in the size of the thrombus; however, the subsequent substitution of rivaroxaban (oral treatment with a direct Factor Xa inhibitor) for warfarin ultimately resolved the thrombosis.

Key words: atrial fibrillation, anticoagulant, cancer, thrombus, warfarin

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Introduction

Novel oral anticoagulants (NOACs) represent alternatives to warfarin anticoagulation for the prevention of non-hemorrhagic stroke and systemic embolic events in patients with non-valvular atrial fibrillation, particularly as NOACs are generally associated with a lower risk of intracranial bleeding than warfarin (1). However, the efficacy of NOACs in resolving established intracardiac thrombi has yet to be validated. Moreover, there are no data regarding the differences in efficacy between NOACs and warfarin in terms of treating established thrombi.

The present report describes a case of a warfarin-resistant right atrial thrombus that developed in the context of non-valvular atrial fibrillation and resolved after the initiation of oral treatment with the direct Factor Xa (FXa) inhibitor rivaroxaban.

Case Report

A 72-year-old man was referred to our department after discovering a right atrial mass. His past medical history was notable for subarachnoid hemorrhage caused by a cerebral artery aneurysm at 58 years of age. In addition, his mother had died of cerebral infarction, and his elder sister had died of myocardial infarction. The patient had undergone colectomy for colon adenocarcinoma with multiple liver metastases at 68 years of age and subsequently received several chemotherapy regimens, including FOLFOX (calcium folinate and fluorouracil), FOLFILI (calcium folinate, fluorouracil, and irinotecan), XELOX, bevacizumab and cetuximab. After chemotherapy, surgery for liver metastasis was performed at 69 years of age. At 71 years of age, lung metastasis developed, and he consequently underwent further surgery. Approximately 10 months after surgery for the lung metastasis, contrast-enhanced chest computed tomography (CT) demonstrated recurrent liver metastasis and a right atrial mass (diameter, 27 mm). In addition, electrocardiography showed atrial fibrillation (AF), which had been known to be present for 10 years, and a chest X-ray revealed cardiomegaly, with a cardiothoracic ratio of 60%. Echocardiography was normal, except for the right atrial mass. Deep vein thrombosis was not detected on contrast CT at that time. The patient therefore received valsartan (40 mg) for hypertension and aspirin (100 mg) for stroke prevention, although

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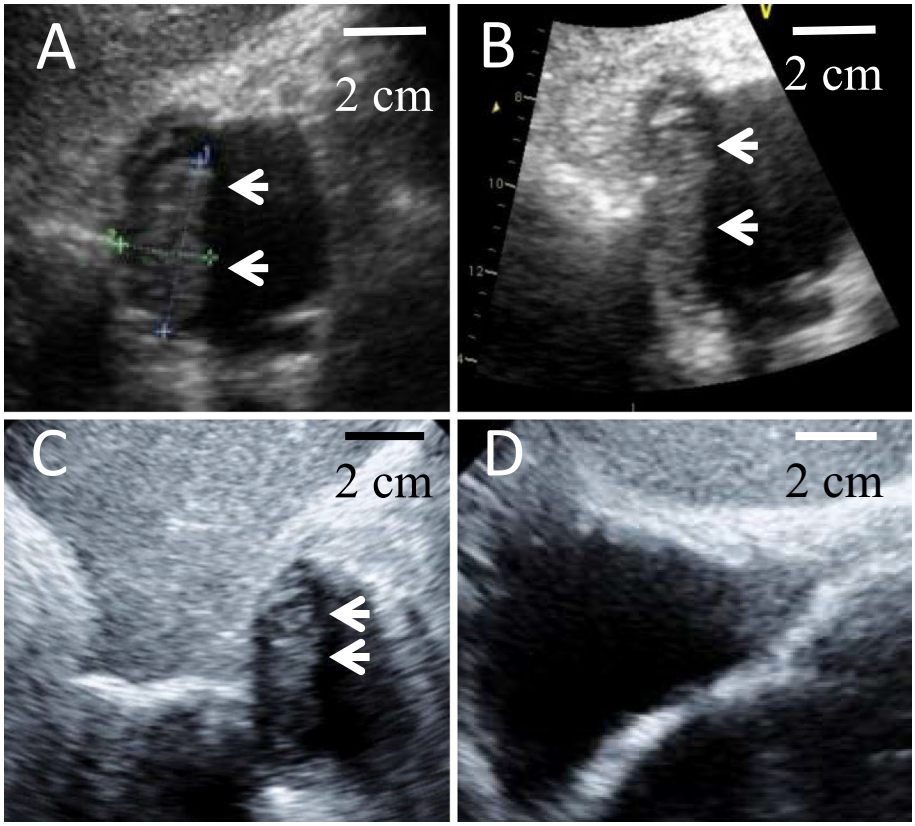

Figure 1. Time course of the right atrial thrombus observed on transthoracic echocardiography (TTE). A) The right atrial thrombus (arrows) was detected on TTE (subxiphoid view). B) The size of the thrombus had not change approximately six weeks after the repeat administration of warfarin. C) The size of the thrombus decreased two weeks after the initiation of rivaroxaban. D) No thrombi were detected four weeks after the start of rivaroxaban therapy.

he was not started on anticoagulant therapy by his home doctor. The platelet count was 53,000/μL, the prothrombin time international normalized ratio (PT-INR) was 1.07, the activated partial thromboplastin time (APTT) was 30.9 s (normal range: 25.2-34.4), the fibrinogen level was 289 mg/dL (normal range: 168-329), the fibrinogen degradation product (FDP) level was 7.5 μg/mL (normal range: <5) and the D-dimer level was 5.6 μg/mL (normal range: <1). Surgical removal was performed as a therapeutic and diagnostic option, and the mass was pathologically diagnosed as a thrombus. The patient's CHA_2DS_2-VASc score was 3 ($CHADS_2$ score of 2), and no further hemorrhagic events were observed.

After the surgery, the patient was treated with warfarin (2.5 mg) in order to achieve a PT-INR of approximately 2.0. He was also given bisoprolol (2.5 mg), furosemide (20 mg) and candesartan (4 mg) for heart failure due to AF with tachycardia. Two months later, the metastatic liver tumor was removed. Subsequent contrast-enhanced chest CT did not show any thrombi in the bilateral atria. After four months, however, he developed angina pectoris, and coronary angiography showed 99% stenosis at segment 6 of the left ascending coronary artery. After changing the warfarin to the continuous intravenous infusion of heparin, bare-metal stent implantation was successfully performed, with the subsequent administration of aspirin (100 mg) and clopidogrel (75 mg). The HAS-BLED score was 3, which indicated a high risk of bleeding. The patient also displayed mild hemoptysis two weeks after the initiation of these agents; therefore, the dose of warfarin was transiently interrupted. One month after stent implantation, the clopidogrel therapy was terminated, and the warfarin (2.5 mg) was restarted. However, the patient's PT-INR was 1.2 at that time, and a thrombus was detected in the right atrium on transthoracic echocardiography (TTE) (Fig. 1A) and contrast-enhanced chest CT (Fig. 2A). Transesophageal echocardiography was not performed because a small abdominal aortic aneurysm with an ulcer-like projection had been detected on CT. Two weeks after the start of warfarin (2.5 mg), the PT-INR was 1.87 (Fig. 3). Therefore, the dose of warfarin was increased to 3.0 mg. After six weeks of increased warfarin therapy (3.0 mg, PT-INR: 2.20) (Fig. 3), the size of the thrombus did not change on TTE (Fig. 1B). The patient did not experience any bleeding sequelae, such as hemoptysis. However, CT suggested the development of a new small intratracheal mass. Because additionally increasing the warfarin dose in order to resolve the thrombus was thought to carry a greater risk of bleeding from the lesion, suspected of metastasis, therapy with the direct FXa inhibitor rivaroxaban was started at a dose of 15 mg once daily. The patient's body

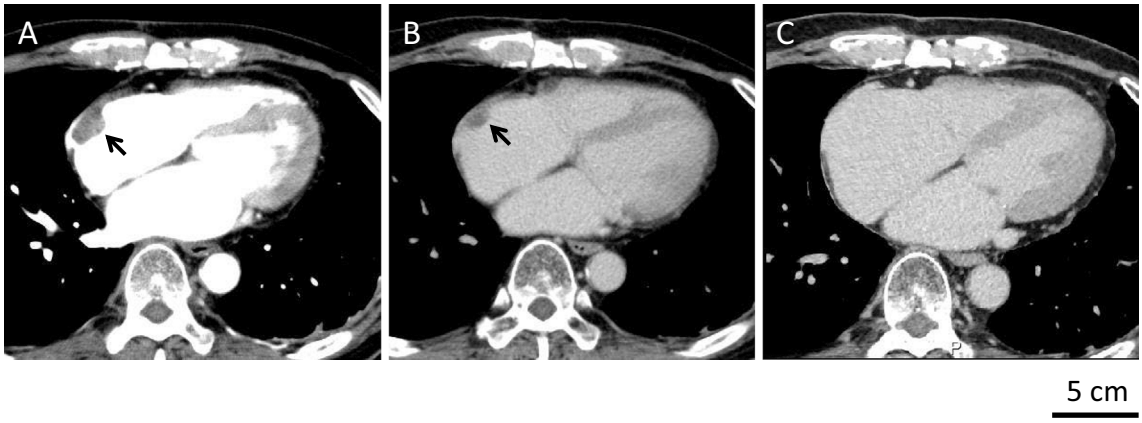

Figure 2. **Time course of the right atrial thrombus observed on contrast-enhanced chest computed tomography (CT). A) The right atrial thrombus (arrow) was detected on chest CT. B) The size of the thrombus decreased four weeks after the start of rivaroxaban. C) No thrombi were detected approximately 10 weeks after the start of rivaroxaban therapy.**

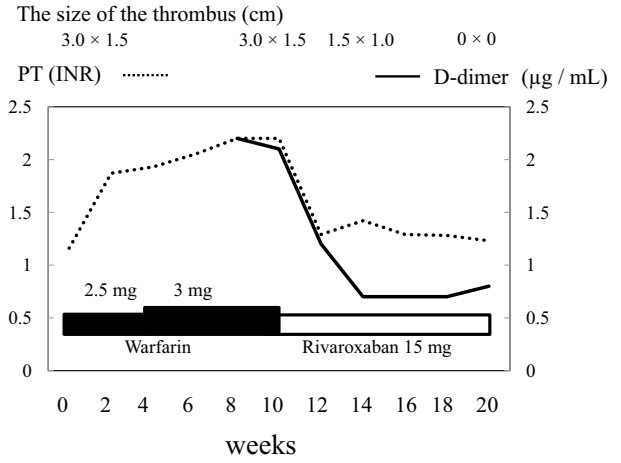

Figure 3. **Clinical course of the anticoagulant therapy and time course of the prothrombin time and D-dimer level.**

weight was 63 kg, his serum creatinine level was 0.72 mg/dL and his Ccr level was 64 mL/min. The size of the thrombus subsequently decreased two weeks after the initiation of rivaroxaban (Fig. 1C), and TTE showed the resolution of the thrombus four weeks after the start of rivaroxaban therapy (Fig. 1D). Meanwhile, CT showed only a small mural thrombus four weeks after the start of rivaroxaban treatment (Fig. 2B), and follow-up CT performed two months after the initiation of rivaroxaban therapy showed the complete resolution of the thrombus (Fig. 2C). After changing the medication to rivaroxaban, the D-dimer level decreased (from 2.1 to 1.2 μg/L) and ultimately normalized (between 0.7 and 0.8 μg/L) (Fig. 3). However, the patient experienced daily hemoptysis under treatment with rivaroxaban. In addition, the size of the intratracheal mass increased to 5 mm, and the lesion was ultimately diagnosed as a metastasis of colon cancer. After surgically removing the metastatic tumor, the patient's hemoptysis resolved, and he was able to tolerate rivaroxaban therapy.

Discussion

Only five case reports involving the resolution of an intracardiac thrombus in response to NOACs have been reported (2-6). Among these cases, thrombosis occurred in the left atrial appendage in four patients with atrial fibrillation (2-4, 6) and within a left ventricular apical aneurysm in a patient with mid-ventricular obstructive hypertrophic cardiomyopathy (5). With respect to treatment, the oral administration of the direct thrombin inhibitor dabigatran was used in three cases, while that of a direct FXa inhibitor was used in two cases (rivaroxaban in one case and apixaban in the other). Only one previous case report demonstrated the resolution of a vitamin-K antagonist-resistant thrombus in the left atrial appendage in response to rivaroxaban therapy (4). In one case, warfarin was replaced with dabigatran because the PT-INR was in the range of 1.5-1.7 in response to treatment with warfarin at a dose of 35 mg/week (2). The remainder of the patients received NOACs as the first-line therapy (3, 5, 6). To the best of our knowledge, this is the first case of the resolution of an atrial thrombus resistant to ordinary control with warfarin in response to rivaroxaban therapy in Japan.

Although Hammerstingl et al. (4) reported that, in contrast to indirect acting vitamin-K antagonists, FXa inhibitors have the potential to both prevent de novo thrombus formation and resolve established thrombi by directly inhibiting the actions of free and thrombus-associated FXa, it remains unclear why rivaroxaban was superior to warfarin in resolving the thrombus located in the right atrium in the present case.

Warfarin is highly effective at antagonizing the vitamin K-dependent clotting pathway mediated by a reduced activity of the four coagulation factors (II, VII, IX and X). This drug also inhibits the vitamin K-dependent gamma-carboxylation of proteins C and S, both of which have anticoagulant effects. Therefore, warfarin also exerts a potential

thrombogenic effect by inhibiting the activities of these anticoagulant proteins.

de Fouw et al. (7) demonstrated that activated protein C promotes fibrinolysis in normal plasma, but not Factor X- or VIII-deficient plasma. These data suggest that rivaroxaban may have a stronger fibrinolytic effect via protein C activation than warfarin.

Recently, Varin et al. (8) demonstrated that rivaroxaban decreases thrombin generation and induces the modification of the fibrin network, characterized by a looser plasma fibrin network with thicker fibers and larger pores. These changes subsequently result in greater permeation of the flow through the clots, rendering them more sensitive to the effects of fibrinolytic enzymes.

The ability of FXa inhibitor to resolve established intracardiac thrombi may vary with according to specific patient characteristics, such as the presence of renal insufficiency (4). The present patient had cancer, which can increase the risk of thrombosis in patients with AF; however, cancer is also associated with an increased risk of hemorrhage. Therefore, the response to anticoagulation may not be predictable in patients with cancer and likely varies from that observed in patients without malignancy (9).

The pathomechanisms of blood coagulation activation in cancer patients are not fully understood; however, the tumor-specific activation of FX may be an important step in the blood coagulation cascade activation in patients with cancer (10, 11). Hence, FXa inhibitors may be more specific anticoagulants than warfarin in patients with cancer. Further research is needed to elucidate the precise indications and mechanisms underlying the superiority of FXa over warfarin in treating established intracardiac thrombi.

In conclusion, rivaroxaban may be useful for resolving intracardiac thrombi resistant to ordinary control with warfarin in some patients with atrial fibrillation.

The authors state that they have no Conflict of Interest (COI).

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