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MINI-FOCUS ISSUE: HEART FAILURE

BEGINNER

CASE REPORT: CLINICAL CASE

Recurrent Left Ventricular Thrombus Formation on Rivaroxaban Therapy in Cardiomyopathy and Liver Cirrhosis

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ABSTRACT

Left ventricular (LV) thrombus in patients with reduced LV systolic function carries significant thromboembolic risk. Direct oral anticoagulants are an attractive alternative to warfarin for LV thrombus management. However, there are not enough data regarding the safety and efficacy of direct oral anticoagulants for the treatment of LV thrombus. (**Level of Difficulty: Beginner.**) (J Am Coll Cardiol Case Rep 2020;2:1501–4) © 2020 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

HISTORY OF PRESENTATION

A 50-year-old man with a history of nonischemic dilated cardiomyopathy with left ventricular (LV) ejection fraction of 15% initially complicated by LV thrombus formation was treated with warfarin. Two repeat echocardiograms showed successful thrombus resolution. Furthermore, warfarin was switched to rivaroxaban because of difficulties in achieving a steady therapeutic international normalized ratio level. Two months later, the patient presented to the hospital with sudden onset of right-sided weakness and altered mental status. Physical exam revealed lethargy, aphasia, spatial neglect to the right side, gaze preference to the left, and right hemiplegia, and Glasgow coma scale 10 to 15 (eye subscore: 5, verbal subscore: 1, motor subscore: 5). Eye examination showed equal and round pupils reactive to light. A cardiovascular exam revealed normal rate, regular rhythm, and normal heart sounds. Vital signs were normal: blood pressure 113/83 mm Hg, pulse 78 beats/min, temperature 97.8°F (36.6°C), respiratory rate 20/min, and 98% oxygen saturation at room air.

LEARNING OBJECTIVES

- Patients with severe LV systolic dysfunction and history of LV thrombus should be continued on anticoagulation for life to prevent recurrent LV thrombus formation and systemic thromboembolism.
- Rivaroxaban should not be used in liver cirrhosis patients, as drug metabolism, thrombin, von Willebrand factor, and albumin levels are altered in liver disease.
- To date, warfarin and low-molecular-weight heparins should be used in patients with liver cirrhosis to treat and prevent LV thrombus.

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ABBREVIATIONS AND ACRONYMS

DOAC = direct oral anticoagulant

LV = left ventricular

PAST MEDICAL HISTORY

The patient had well-controlled diabetes mellitus, arterial hypertension, compensated heart failure, history of implantable cardioverter-defibrillator, compensated alcoholic liver cirrhosis, hyperlipidemia, and chronic punctuated infarcts of the right occipital lobe, left superior cerebellum, and left superior frontal gyrus.

DIFFERENTIAL DIAGNOSIS

Based on patient presentation, the differential diagnosis included thromboembolic stroke from de novo LV thrombus versus intracranial bleeding versus thromboembolic stroke because of paroxysmal atrial fibrillation.

INVESTIGATIONS

Initial head computed tomography and angiography revealed acute left occipital and left middle cerebral artery territory infarcts and left M1 occlusion (**Figures 1A and 1B**); echocardiography showed large apical LV thrombus (**Figure 2**, Videos 1 and 2).

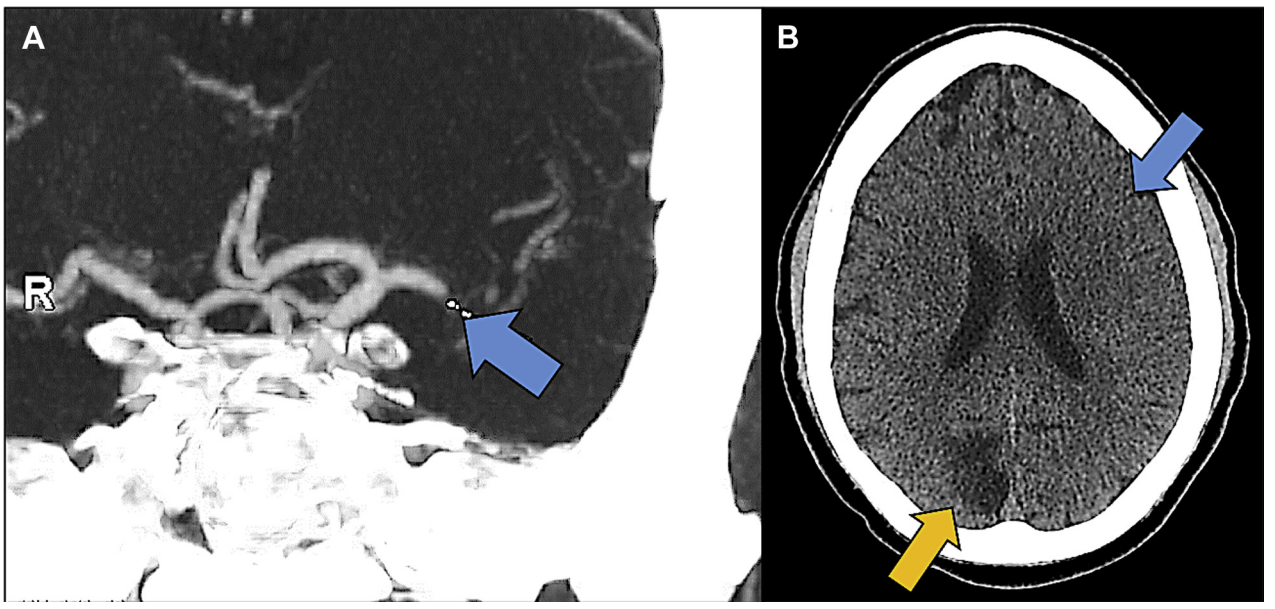
MANAGEMENT

The patient was not a candidate for tissue plasminogen activator treatment (owing to rivaroxaban use) or thrombectomy (ASPECTS [Alberta Stroke Program Early CT Score] of 4; endovascular therapy is recommended in patients with baseline ASPECTS ≥6) (1). Given LV thrombus and high risk for recurrent stroke, neurology recommended intravenous heparin infusion. Six hours after heparin was started, the patient's status deteriorated; he developed acute respiratory failure and was intubated. Absences of gag, pupillary, and corneal reflexes were noted. Repeat computed tomography of the head revealed massive parenchymal hemorrhage and vasogenic edema with a left-to-right 2-cm midline shift. Hemorrhage extended into the bilateral lateral ventricles, with enlargement of the occipital and temporal horns of the lateral ventricles (**Figure 3**).

DISCUSSION

Severe LV systolic dysfunction often leads to LV thrombus formation. Thromboembolic events occur in 10% to 40% of patients with LV thrombus and no anticoagulation. Currently, the American Heart Association and the European Society of Cardiology recommend warfarin for patients with LV thrombus

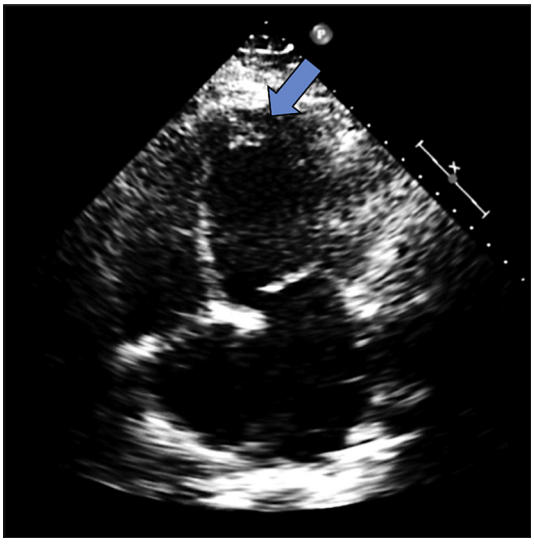
FIGURE 1 Acute Strokes of Left Frontal and Occipital Lobes and Left M1 Cerebral Artery Occlusion



(A) Computed tomography angiography of cerebral arteries. The **blue arrow** depicts left M1 occlusion. **(B)** Computed tomography of the head, axial view. The **blue arrow** indicates M1 territory acute infarct (loss of gray-white matter differentiation), and the **yellow arrow** depicts chronic left occipital infarct (encephalomalacia).

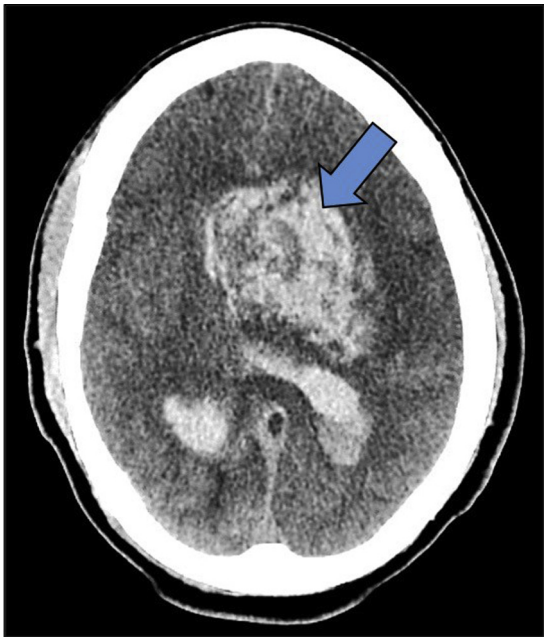
based on observational studies. The 2014 American Heart Association stroke guidelines recommended direct oral anticoagulants (DOACs) in patients with LV mural thrombus as an alternative to warfarin (Class IIb, Level of Evidence: C) (2). Multiple cases of LV thrombus resolution with rivaroxaban have been reported (3). Additionally, a recent meta-analysis of case reports of DOACs for the treatment of LV thrombus reported LV thrombus resolution in 45 patients and failure to resolve in 4 patients (4). Degheim et al. (2) reported LV thrombus formation on rivaroxaban in patients with nonischemic cardiomyopathy. Our case raises concern over the efficacy of DOACs in the management of LV thrombus in patients with liver cirrhosis who are thought to be in a procoagulant state and thus prone to thrombus formation. The liver synthesized anticoagulant, such as protein C and S, antithrombin III, as well as fibrinolytic factors that are not measured in routine blood assays. Moreover, the cirrhotic liver cannot clear von Willebrand factor, leading to an abnormally high level of von Willebrand factor, which further adds to the prothrombotic effects of cirrhosis (5). Rivaroxaban is 65% metabolized by the liver, and in cirrhosis P450-mediated DOAC metabolism is altered leading to a change in pharmacokinetics to various degrees. Previous studies have shown that rivaroxaban resulted in a reduced anticoagulant effect in deep venous thrombosis treatment in Child-Turcotte-Pugh class C cirrhosis patients, suggesting the limitations of DOACs use (6). Potze et al. (7) did not recommend rivaroxaban use in patients with Child-Turcotte-Pugh class B and C cirrhosis as well, owing to reduced anticoagulant effect in vitro with standard DOAC dosage, and suggested factor X plasma level monitoring in cirrhotic patients (5). For portal vein thrombosis, Basili et al. (8) recommended low-molecular-weight heparins instead of DOACs. Hence, current evidence does not support the routine use of DOACs in these patients (8). Respectively, in patients with liver cirrhosis and atrial fibrillation, the use of DOACs was associated with fewer bleeding events compared with warfarin (9). Despite the practical advantages of rivaroxaban (predictable dosing, no requirement for a regular blood draw for international normalized ratio monitoring, no dietary restrictions, and minimal drug interactions), the use of rivaroxaban in standard dose cannot be recommended in cirrhotic patients because of lack of evidence that any DOAC prevents systemic thromboembolism. Currently, there is 1 ongoing clinical trial aimed to investigate the efficacy of apixaban versus warfarin in patients with LV thrombus who have suffered a recent myocardial infarction (NCT03232398) and 2

FIGURE 2 Enlarged Heart With Large Apical Mural Thrombus in the Left Ventricle



Transthoracic echocardiography, apical 4-chamber view. The **blue arrow** depicts a large apical thrombus.

FIGURE 3 Large Intracerebral Hemorrhage With Ventricular Extension and Vasogenic Edema



Computed tomography of the head, axial view. The **blue arrow** indicates a large parenchymal hemorrhage in the left frontal lobe. With vasogenic edema and right-to-left midline shift, the hemorrhage extends into bilateral lateral ventricles and occipital and temporal horns.

trials (NCT02643212, NCT03193502) that will study the effects of rivaroxaban in patients with liver cirrhosis. Perhaps these studies will help to establish the patient population with liver cirrhosis and LV thrombus that will benefit from DOACs and the correct drug dosage.

CONCLUSIONS

Patients with a history of LV thrombus and liver cirrhosis should be treated with warfarin or low-molecular-weight heparins. Further studies are necessary to confirm or refute the safety and efficacy of LV thrombus treatment with DOACs in cirrhotic patients.

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KEY WORDS cirrhosis, LV thrombus, oral anticoagulation, rivaroxaban

APPENDIX For supplemental videos, please see the online version of this paper.