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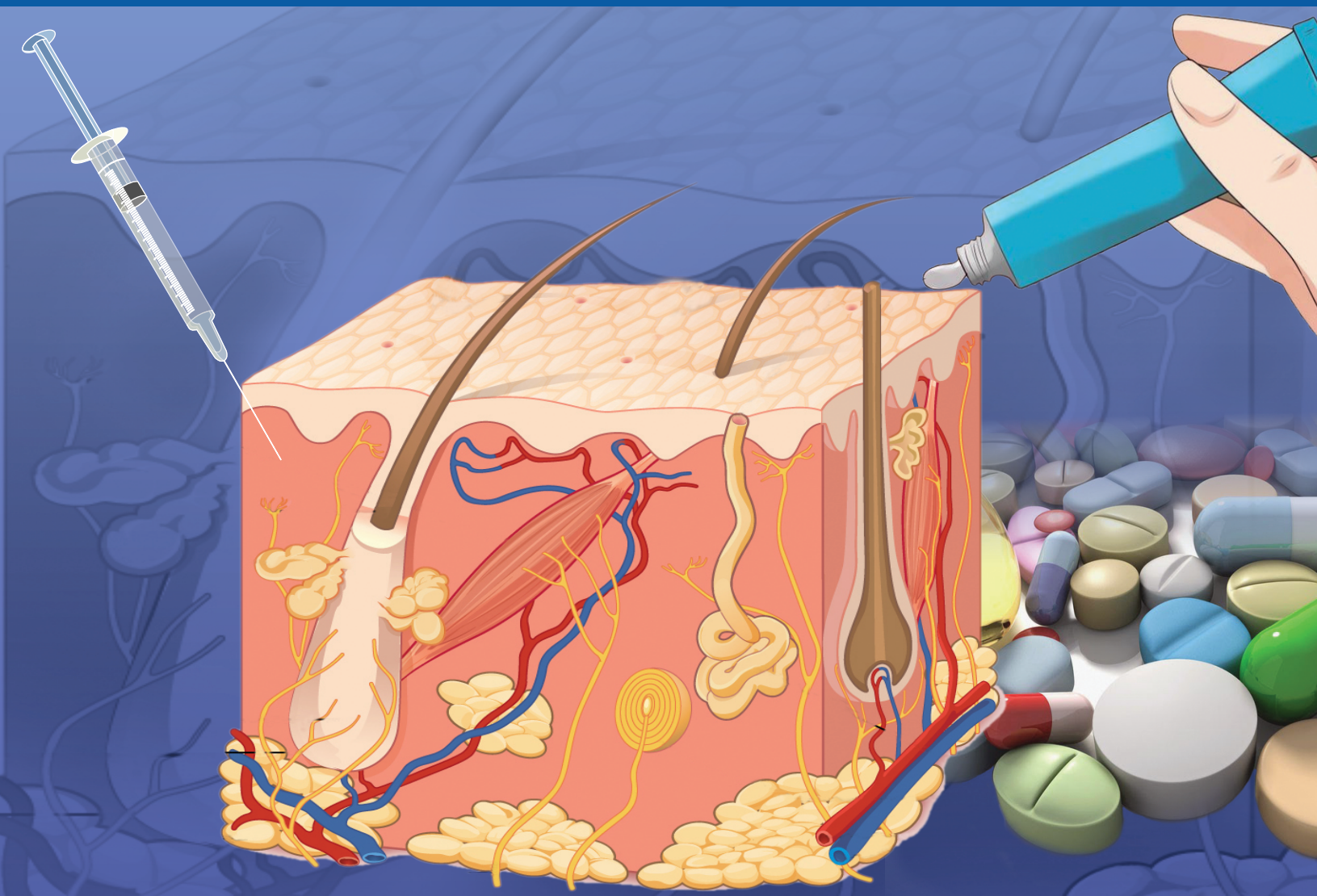

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Case Report

Recalcitrant livedoid vasculopathy: A successful treatment with oral rivaroxaban

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Abstract

Livedoid vasculopathy (LV) is a chronic prothrombotic disease of cutaneous microcirculation resulting in cutaneous ischemia and infarction. Chronic disease often results in painful ulcerations and atrophie blanche on the lower extremities, predisposing affected patients toward infection and high morbidity. Treatment of LV is often difficult and prolonged. Owing to the postulated pathophysiology of vasculopathy, rivaroxaban has been recently suggested as a treatment modality and seems to induce significant improvement in some patients. Compared with other treatments such as classic anticoagulants or intravenous immunoglobulin, rivaroxaban is far more convenient as it does not require injection, international normalized ratio monitoring or hospitalization. Herein, we report the successful treatment of recalcitrant LV in two Indian patients with oral rivaroxaban along with a review on use of rivaroxaban in LV.

Keywords: Chronic leg ulceration, oral rivaroxaban, recalcitrant livedoid vasculopathy

Introduction

Livedoid vasculopathy (LV) is a rare thrombo-occlusive disease with an estimated incidence of ten cases per million.[1] LV presents with painful, recurrent, and recalcitrant ulcerations of the legs, which result in irreversible scarring. The pathogenesis is not certain, but dermal thrombosis is believed to play a primary role. Various systemic coagulopathies, including antiphospholipid syndrome, dysproteinemias, genetic thrombophilic disorders, such as Factor V Leiden (R506Q) mutation, deficiency in protein C or S, hyperhomocysteinemia, and other disorders of abnormal platelet activation or fibrinolysis have also been observed in patients with LV.[2] Therapeutic options are multiple including subcutaneous low molecular weight heparin, warfarin, aspirin, dipyridamole, pentoxifylline, nifedipine, sulfasalazine and intravenous immunoglobulin, among others, although none are well established.[3] Recently, rivaroxaban, a direct factor Xa inhibitor, which can be taken orally and requires no laboratory monitoring, was shown to be effective in the treatment of LV. The current report describes two cases with recalcitrant LV and chronic leg ulcerations receiving oral rivaroxaban with significant improvement after treatment.

Case Report

Case 1

A 30-year-old woman presented with recurrent ulcers on both legs since a duration of 4 years. Cutaneous examination revealed multiple ulcers of varying size having well-defined erythematous borders, sloping edges associated with pus and scabs with few atrophic scars over dorsum of both feet and ankles [Figure 1A and B]. There was no history of trauma, photosensitivity, or family history of similar complaints. There was no evidence of pustular lesions or pathergy phenomenon. Laboratory analyses showed normal levels of blood platelet count, erythrocyte sedimentation rate (ESR), c-reactive protein (CRP), alanine aminotransferase (ALT), and creatinine

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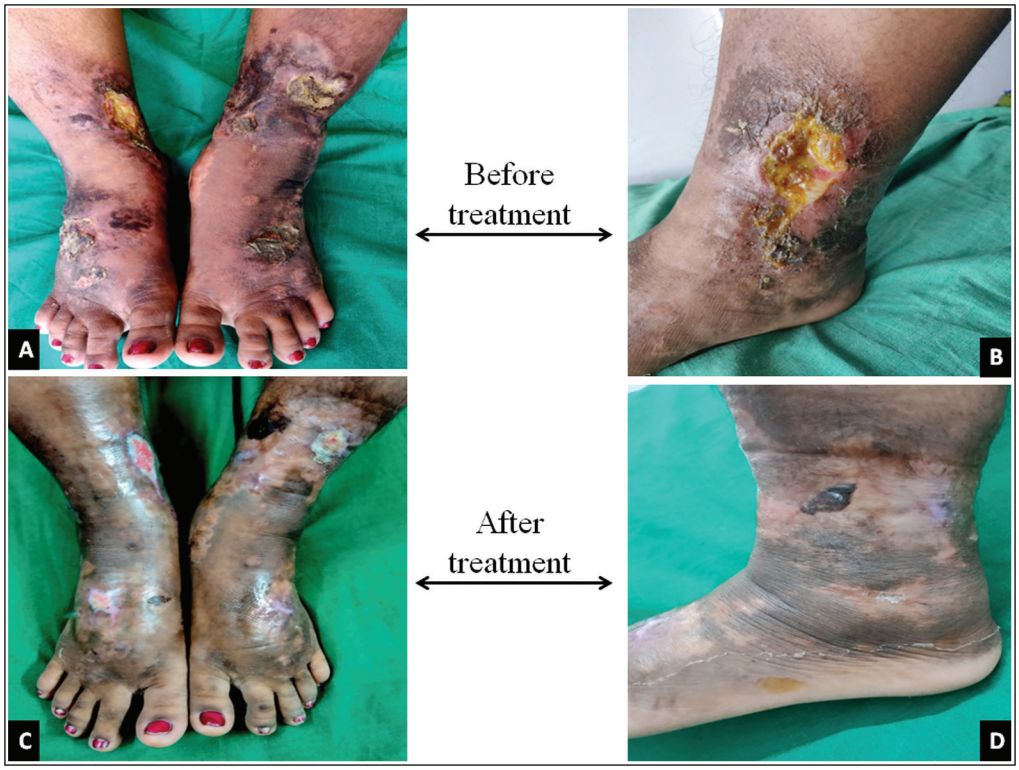

Figure 1: Case 1 (A and B) Multiple ulcers having well-defined borders, sloping edges associated with purulent discharge, and scabs over dorsum of both feet and ankles. (C and D) After 6 weeks of oral rivaroxaban ulcers are significantly decreased in size

and negative anticardiolipin antibodies (ACLA), and Mantoux test. Homocysteine, protein C and S were also within normal limits. Histopathology from lesion showed intravascular thrombus without perivascular inflammation in the superficial and mid dermis associated with dermal fibrosis confirming a diagnosis of LV [Figure 2A and B].

She received oral and topical antibiotics with colchicine, pentoxyfylline, with aspirin and clopidogrel for two and half years without significant improvement. We started oral rivaroxaban (10 mg) twice daily in addition to vitamin C and pentoxyphylline (400 mg BD) with debridement of necrotic tissue of ulcers and dressing. After 6 weeks of treatment ulcers significantly improved and almost completely healed without appearance of new lesions [Figure 1C and D]. After clearance of the lesions rivaroxaban was tapered to 10 mg once daily for 1 month and then alternate day for 1 more month. We had continued vitamin C tables and pentoxyphylline (400 mg BD) for next 3 months to prevent relapse. She is on regular follow-up since last 1 year; till now no relapse of lesions is noted.

Case 2

A 28-year-old man presented with recurrent ulcerations and swelling of feet since a duration of 12 years. Cutaneous examination revealed multiple punched out ulcers on dorsal aspect of feet with whitish atrophic scars [Figure 3A and B]. There was no family history of similar complaints. He did not have any systemic complaints. Laboratory investigations including complete blood count, platelets, ESR, CRP, liver function tests (LFT), renal function tests (RFT), protein C and S were within normal limits and negative ACLA. His homocysteine level was elevated: 28.5 micromol/L (normal: 5.4–16.22 micromol/L). Histopathology of lesion showed fibrin occlusion, hyalinization, thickened vessel wall, and thrombus formation in upper dermal vessels with minimal perivascular lymphocytic infiltrate [Figure 4A and B]. On basis of clinical and investigational evidence he was diagnosed as a case of LV.

Patient had been treated with multiple courses of topical and systemic treatments including antibiotics, colchicine, aspirin, clopidogrel without much relief. He was started on oral rivaroxaban (10 mg) twice daily with aspirin (75 mg OD). After 4 weeks of treatment lesions significantly improved with almost complete healing of ulcerations [Figure 3C and D], then rivaroxaban was continued for next 2 months with aspirin (75 mg OD) to prevent relapse. After that rivaroxaban dose was reduced to 10 mg once daily for one and half month then alternate day for 1 more month. On regular follow-up of 5 months, he did not show relapse and no any side effects of rivaroxaban was noted.

Discussion

LV is a disease that generally affects the lower extremities and is most commonly seen in young to middle-age women.

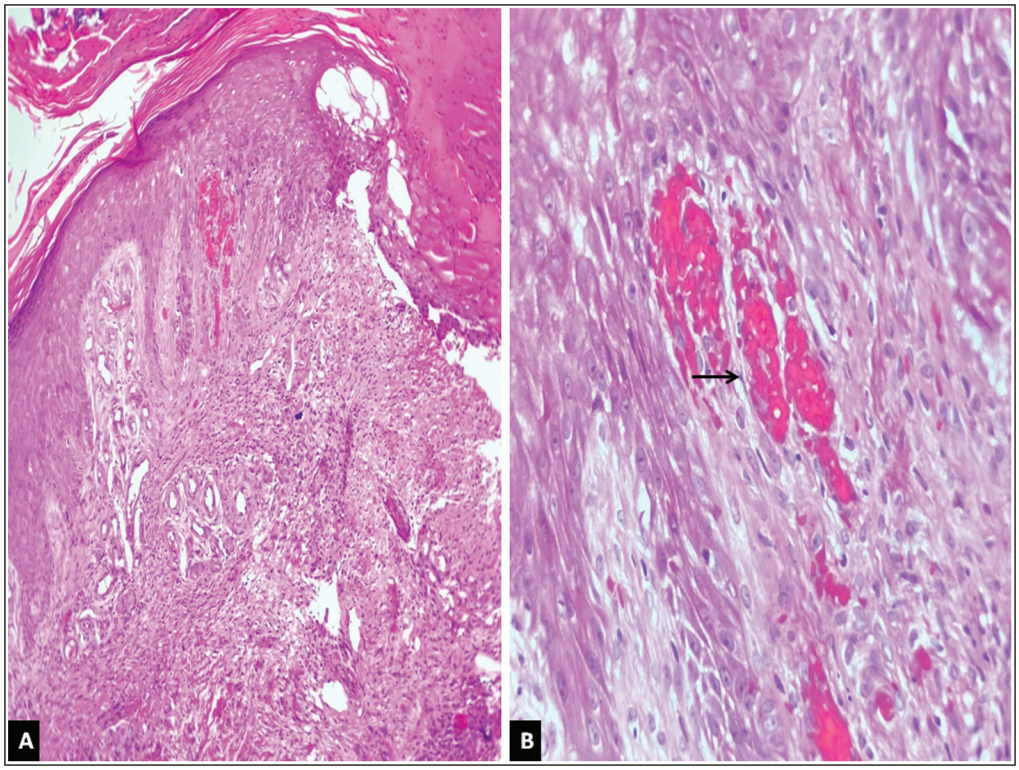

Figure 2: Case 1 (A) Biopsy showing proliferation of superficial dermal vessels with intravascular thrombus and minimal perivascular inflammation associated with dermal fibrosis (HandE, x100). (B) Thrombus formation in superficial dermal vessels without inflammation (black arrow) (HandE, x400)

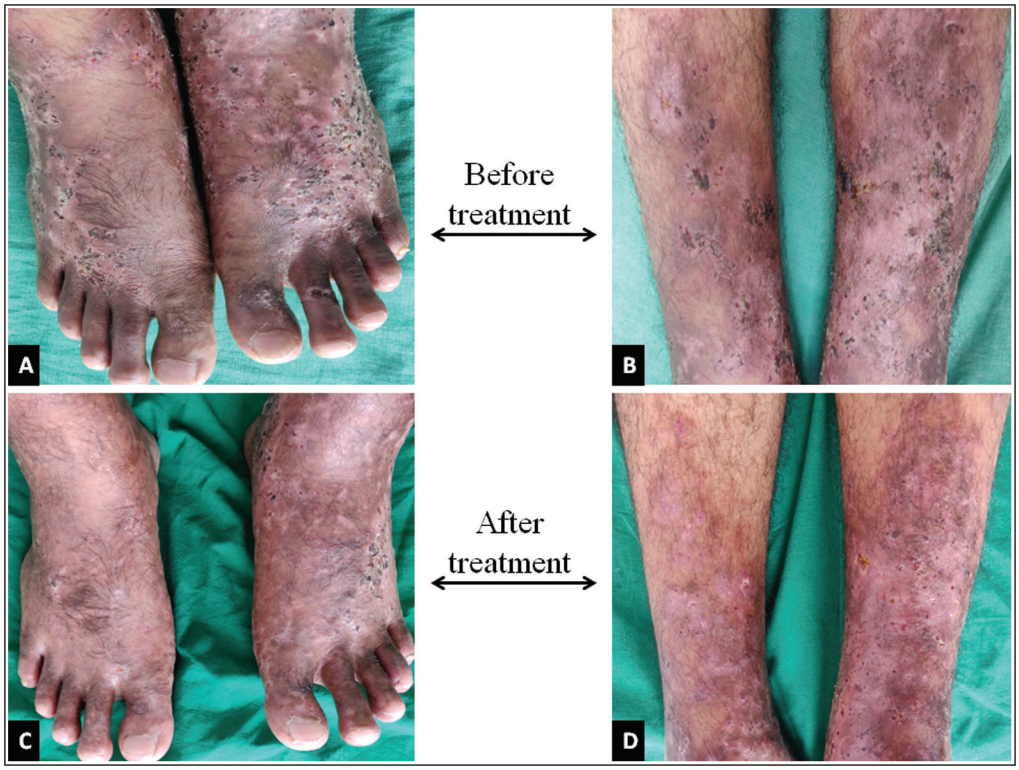

Figure 3: Case 2 (A and B) Multiple punched out ulcers with crusts on dorsal aspect of feet and shin few of them healing with whitish atrophic scars. (C and D) After 4 weeks of rivaroxaban almost all ulcers are healed with scars

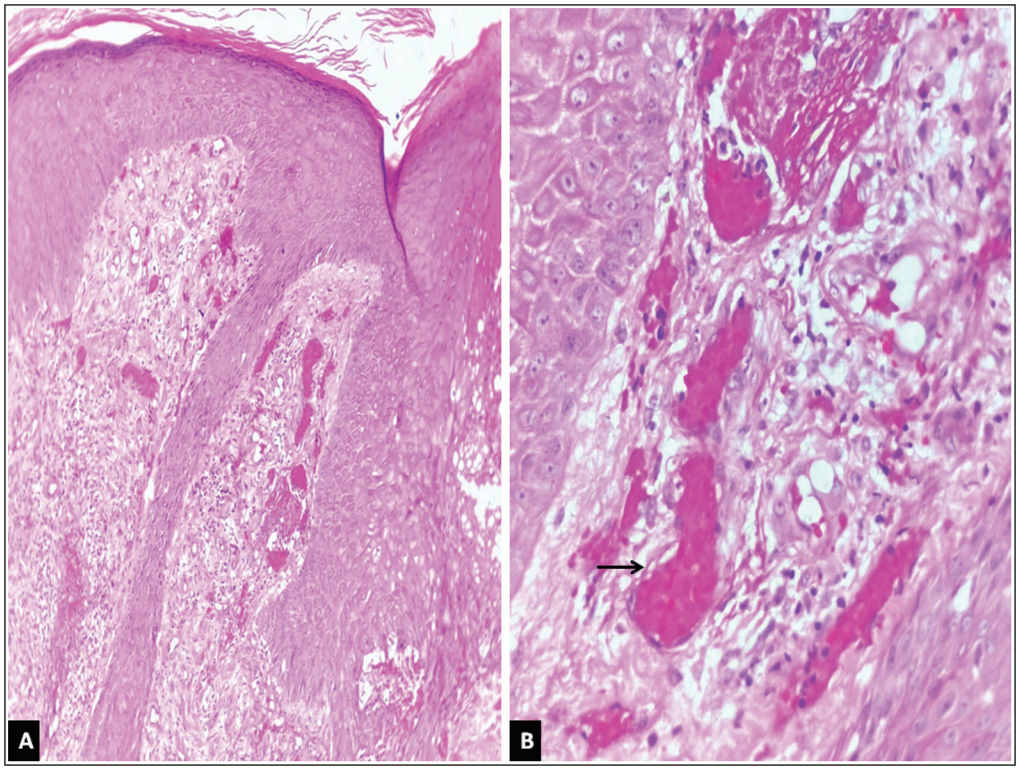

Figure 4: Case 2 (A) Biopsy showing vascular proliferation and thrombus formation in upper dermal capillaries with minimal perivascular lymphocytic infiltrate (HandE, x100). (B) Superficial dermal vessels having hyalinization, thickened vessel wall, and thrombus formation without inflammation (black arrow) (HandE, x400)

The pathogenesis of LV is cutaneous ischemia and infarction caused by the occlusion of capillary microcirculation.[4] Perivascular inflammatory infiltration is secondary to the inflammation in an advanced stage and less prominent in comparison to the vascular occlusion.[5] LV is almost exclusively located on both lower limbs, particularly around ankles and dorsal aspect of feet. Characteristic appearances of LV include one or more of following triad: livedo racemosa, ulceration, and atrophie blanche. Ulceration develops as the result of cutaneous ischemia in the acute stage of LV.[3] Atrophie blanche is an irreversible scarring representing the remnants of cutaneous infarction at the end of the restructuring process.

Laboratory investigations for LV include investigations for diseases which are known to have prothrombotic states such as autoimmune diseases like immune thrombocytopenic purpura and systemic lupus erythematosus, neoplastic syndromes, congenital abnormalities of the fibrinolytic system, homocysteinemia, protein C and S deficiency. It is not uncommon to find one or more thrombophilic conditions in cases of LV. Our second case had secondary hyperhomocysteinemia.

Case reports predominantly suggest low-molecular-weight heparin and warfarin as therapeutic options, based on the underlying pathophysiological phenomena of the vasculopathy with microthrombosis.[6] However, no studies have provided a consensus for the optimal LV treatment.

The most recent data suggest that the oral Factor X inhibitor rivaroxaban can successfully prevent cutaneous ulcerations and ischemic pain in patients with LV.[3] Rivaroxaban inhibits Factor Xa and Factor Xa/Factor Va complex (prothrombinase) activities, preventing conversion of prothrombin to thrombin.[7] Rivaroxaban is tolerated better than heparin and warfarin therapy, which require daily subcutaneous injections and regular blood testing, respectively. Rivaroxaban can be taken at a fixed dose without routine monitoring because the pharmacokinetics and pharmacodynamics are predictable.[7]

Rivaroxaban in dosage of 10 mg twice daily led to rapid improvement in both of our patients with rapid resolution of pain and the size of ulcers. The first patient's pain resolved within 2 days, and the ulcers almost completely healed in 6 weeks. The second patient noted considerable relief in his pain and complete healing of his ulcers within 4 weeks of starting rivaroxaban (10 mg twice daily). In both patients previous medications had failed to give resolution especially in second patient who had not experienced complete resolution of lesions during a long duration of 12 years.

There were no adverse effects, such as hemorrhages/bleeding tendency. There was no recurrence of symptoms

during a follow-up of 1 year in first case and 5 months in second case.

Rivaroxaban thus may be considered a convenient, effective and safe treatment in LV, including long-term recalcitrant disease.

Thus larger trials of rivaroxaban are warranted in patients with recalcitrant LV, in the presence or absence of known coagulopathy.

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Conflicts of interest

There are no conflicts of interest.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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