Abstract
We hereby present our experience of low-dose oral warfarin in the management of three cases of livedoid vasculopathy.

KEY WORDS: Anticoagulation, livedoid vasculopathy, medical treatment, warfarin

Introduction
Livedoid vasculopathy (LV) is an uncommon chronic vessel disease characterized by the development of painful ulcers on the distal part of the lower limbs.[1] Painful ulcers develop due to vascular occlusion produced by fibrin thrombi. Livedoid vasculitis term is sometimes used, but since there is no inflammation in the vessel wall, the term “vasculitis” should best be avoided.

The exact cause of the vascular occlusion in LV is still not clear. It can be primary (idiopathic) or secondary to various pro-thrombotic states such as antiphospholipid antibody syndrome, protein C and S deficiency, and homocysteinemia. Most of the reported cases are idiopathic in nature and not associated with any systemic thrombosis and remain restricted to cutaneous small vessels of distal part of lower limbs. Healing of these small ulcers leads to the formation of small atrophic white scars referred to as atrophie blanche.

It is difficult to treat the disorder and often proves recalcitrant to therapy with frequent relapses.[2] Keeping in mind, the potential procoagulant mechanisms involved in the pathogenesis, the aim of the treatment is to prevent the thrombus formation in the cutaneous blood vessels. We hereby report three cases of LV who were successfully treated with low-dose warfarin.

Case Reports
Case 1
A 39-year-old immunocompetent male presented with a 2-year history of highly painful ulcers around both ankle areas. His systemic examination was unremarkable. The patient had received multiple rounds of analgesic and oral corticosteroid in the previous consultation without significant improvement. On examination, multiple small crusted ulcers were present around both the ankles [Figure 1]. Few atrophic thin scars (atrophie blanche) were also evident. Complete hemogram and coagulation profile were within normal limits. Autoantibody profiles were insignificant. Biopsy from ulcer edge showed vascular occlusion due to thrombosis and hyalinizing changes in the vessel wall without significant vascular inflammation [Figure 2]. A diagnosis of LV was made. The patient was prescribed oral betamethasone sodium phosphate 1 mg (Betnesol forte®) in tapering dose and tab warfarin 1 mg/day for a fortnight. Oral steroids were stopped completely after 15 days.
Within 15 days, the patient reported a significant reduction in pain and ulcers showed signs of healing, however, few lesions were still active. The dose of warfarin was escalated to 2 mg daily, and after 2 months all the ulcers showed complete healing [Figure 3]. In this case, warfarin was continued for 6 months. During the treatment with oral warfarin, the patient was regularly monitored with coagulation profile, and his international normalized ratio (INR) remained in the range of 1–1.5.

**Case 2**

A 30-year-old male presented with severely painful ulcers around both ankle for 1½ years. There was no history of significant systemic complaints. In the previous multiple consultation, he had received oral analgesic, antibiotics, corticosteroids, and dapsone without any significant remission. On examination, multiple small ulcers covered with crusts were present near both ankles and dorsal aspect of feet [Figure 4]. His complete hemogram and coagulation profile were within normal reference range. Autoantibody screen was not significant. Biopsy was suggestive of LV. The patient was prescribed betamethasone sodium phosphate 1 mg (Betnesol forte®) in tapering doses for 15 days and oral warfarin 1 mg daily along with topical steroid-antibiotic cream. At the end of 1 month of treatment, the patient reported subsidence of pain and healing of ulcers [Figure 5]. After 1 month, the dose of warfarin was increased to 2 mg/day which patient continued for the next 8 months. During the warfarin therapy, the patient was regularly monitored with coagulation profile. After 8 months of warfarin therapy, the patient discontinued the treatment as he was in clinical remission.

However, the patient presented with recurrence after 1 year of stopping treatment and is being currently receiving oral warfarin 2 mg/day (August 2016).

**Case 3**

An 18-year-old male presented with painful ulcers around both ankles joint of 1½ years duration. On multiple previous occasions, the patient had received oral antibiotics, pentoxifylline, and aspirin without significant improvement. There were no systemic complaints. On examination, there were multiple small crusted ulcers near both ankles extending on to adjoining part of lower legs and dorsal aspect of feet. His complete hemogram and coagulation profile were within normal reference range. Autoantibody screen was not significant. Biopsy was suggestive of LV. The patient was

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**Figure 1:** Typical leg ulcers of livedoid vasculopathy with atrophie blanche in case 1

**Figure 2:** H and E stained sections showing fibrin thrombi in the vessel lumen (×20)

**Figure 3:** Posttreatment results showing ulcer healing in case 1 after warfarin therapy

**Figure 4:** Case 2 showing leg ulcers of livedoid vasculopathy with crusting
prescribed on topical fusidic acid with steroid and oral warfarin 1 mg/day. After 1 month of warfarin therapy, all the lesions healed and warfarin was continued for the next 8 months.

In all the patients, venous duplex ultrasound did not show any signs of venous incompetence and autoantibody panel (antinuclear antibody, antiphospholipid antibody) did not show circulating pathogenic antibodies.

Discussion

Clinically, LV presents with painful small ulcers usually around ankle and gaiter area. The diagnosis is mostly made clinically though biopsy may help to arrive at the diagnosis. Although LV is more common in females, all our patients were young males.

Venous ulcer can be a close differential, but pigmentation classically associated with venous ulcer is usually not seen in livedoid ulcers. Ulcers in LV are ischemic ulcers results from vascular occlusion by fibrin thrombi.[3] What causes the thrombus formation is still unclear. It may be associated with prothrombotic states such as antiphospholipid syndrome and protein C/S deficiency, but most of the cases are idiopathic. In LV, thrombosis affects cutaneous vessels of lower limbs only without any systemic thrombosis. All our three patients had a localized vaso-occlusive disease restricted to skin without any systemic involvement. A detailed laboratory work up for hypercoagulable state in all the patients did not yield any positive result indicating no systemic cause for a localized thrombosis. Since the vessel pathology is devoid of significant inflammation, steroids have limited therapeutic potential. In our patients, we had given a short course of long acting oral steroid to tide over any secondary inflammation.

The pain associated with ischemic ulcers of LV is usually very severe and may require use of opioid analgesics. Various other drugs (aspirin, pentoxifylline, niacin, dipyridamole, and danazol) have been tried for the treatment of LV with limited success.

One of our patients received aspirin and pentoxifylline without much benefit. However, in all the patients, warfarin produced great relief in pain within 15 days.

Thrombus formation is a critical event in the pathogenesis of LV. Warfarin has anticoagulant action, and hence, it is commonly used drug for the treatment of thrombotic disorders (deep venous thrombosis). Coagulation profile needs to be monitored while the patient is on warfarin therapy. Prothrombin time is usually described as ratio INR which compares the ratio of anticoagulation effect with normal value. In systemic thrombotic disorder, the aim is to achieve INR of 2–3. A high INR predisposes the patient to an increased risk of bleeding, however; in LV, not associated with any prothrombotic abnormality, a small dose of warfarin is sufficient to achieve clinical remission. Our patient had INR value within the range of 1–1.5. A small dose of warfarin (1–2 mg/day) was effective in all the three patients without significant raise in INR ratio. The small dose of warfarin fulfils the clinical remission without the risk of abnormal bleeding and was found to be safe in all the three patients.

Warfarin is a slow acting anticoagulant hence the effect is evident after few days. In two patients treated with 1 mg of warfarin dose, the response was inadequate hence the dose was increased to 2 mg which proved to be adequate. No significant side effect was noticed in our patients. LV runs an indefinite chronic course. In our patients, we used warfarin for 8 months with good response. No follow-up details are available for patient 1 and 3; whereas case 2 developed recurrence after 1 year which was again controlled with warfarin. Low-dose warfarin 2 mg/day along with aspirin was successfully used to treat LV associated with antiphospholipid syndrome[4] and in another case 3–5 mg of warfarin was used to treat LV associated with cryofibrinogenemia.[5] The cases are presented to highlight the use of low-dose warfarin in the treatment of LV for which effective therapy is not available.

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Nil.

Conflicts of interest

There are no conflicts of interest.

What is new?

Low-dose warfarin can be used in the treatment of LV with minimal monitoring of coagulation cascade:

• Future RCT are needed to confirm the therapeutic effect of warfarin in LV.

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