Clinical, Laboratory, Histopathological and Therapeutic Profile of Livedoid Vasculopathy: A Case Series of 17 Patients

Abstract
Livedoid vasculopathy is a rare disorder clinically presenting with triad of livedo reticularis, leg ulcerations, and atrophic blanche. We present a case series of 17 patients with clinical and/or histopathologically confirmed livedoid vasculopathy from a single tertiary centre in India with female-to-male ratio of 1.5:1 and mean age of 36.12 ± 12.02 years. Presentation with burning pain around ankles was seen in 83.33% of patients, while 100% had atrophic blanche/scarring and 76.47% had retiform ulcers. Hypercholesterolemia was seen in four patients, while systemic lupus erythematosus (SLE), anti-phospholipid antibody with SLE, dermatomyositis and hyper-homocysteinemia were seen in one patient each. The most common histopathology finding was hyaline thrombi within dermal vessels in 94.11%. On treatment with dual anti-platelet therapy, 70.58% of patients could achieve significant improvement in their Visual Analog Scale, Dermatology Life Quality Index and reduction in ulcer scores without serious adverse events. Out of 17 patients, 11 experienced flare in their disease course over one year period of follow-up. This cohort aims to contribute to Indian literature of this underreported entity.

Keywords: Atrophic blanche, hyalinizing vasculopathy, livedoid vasculopathy

Introduction
Livedoid vasculopathy (LV) is a rare hyalinizing vasculopathy characterised by recurrent occlusion of cutaneous microcirculation resulting in classic triad of livedo reticularis, leg ulcerations, and white atrophic stellate scarring with peripheral telangiectasias known as atrophic blanche. Thrombophilias, autoimmune connective tissue diseases and neoplasms maybe associated.[1] Treatment is challenging and there are no therapeutic guidelines.[2,3]

We present a retrospective case compilation of patients with LV from a single tertiary centre in India focusing on epidemiological, clinical, histopathological and therapeutic profile.

Case Series
This analysis included 17 clinical and/or histopathological confirmed cases of LV from February 2019 to January 2021. All patients underwent the following set of investigations:[1]
- Baseline - Hemogram; liver, renal and thyroid functions, erythrocyte sedimentation rate, C-reactive protein, blood glucose and lipid profile.
- For assessment of procoagulant state - Prothrombin time, activated partial thromboplastin time, fibrinogen, D-dimer, protein C, protein S, anti-thrombin III levels, cryoglobulins, lupus anticoagulant, anti-cardiolipin, anti-beta-2-glycoprotein-I antibodies; homocysteine levels, lipoprotein (a).
- For detection of associated conditions - Anti-nuclear antibodies, anti-Ro, anti-La, serum complement, Vitamin B6, Vitamin B12, Rheumatoid factor, Hepatitis B, C and HIV.
- To rule out underlying causes - Venous doppler, serum and urine protein electrophoresis.

Epidemiological, clinical, laboratory and histopathological profile
Patient characteristics of this cohort are summarized in [Table 1, Supplemental Table 1]. [Figures 1 and 2] show the classical clinical and histopathology findings of LV, respectively.

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Table 1: Clinical, laboratory and histopathological profile of 17 patients with livedoid vasculopathy

| Parameter                      | Patient characteristics |
|--------------------------------|-------------------------|
| Mean age                       | 36.12±12.02 years (Range: 18-58 years) |
| Sex                            |                         |
| Female                         | 64.7% (n=11)            |
| Male                           | 35.3% (n=6)             |
| Female-to-male ratio           | 1.5:1                   |
| Mean duration of disease       | 3.76±2.56 years         |
| Associated factors:            |                         |
| Obesity                        | 23.53% (n=4)            |
| Smoking                        | 11.76% (n=2)            |
| Hypertension                   | 5.89% (n=1)             |
| Clinical presentation:         |                         |
| Site                           |                         |
| Around bilateral malleoli      | 94.11% (n=16)           |
| Around lateral malleolus and extending till buttocks | 5.89% (n=1) |
| Symptoms:                      |                         |
| Burning pain around ankles     | 88.33% (n=15)           |
| Tingling and numbness          | 11.67% (n=2)            |
| Signs:                         |                         |
| Atrophie blanche/scarring      | 100% (n=17)             |
| Retiform ulcers                | 76.47% (n=13)           |
| Telangiectasias/livedoid changes | 35.29% (n=6)        |
| Pedal edema                    | 11.76% (n=2)            |
| Associated diseases:           |                         |
| SLE                            | 5.89% (n=1)             |
| SLE with anti-phospholipid antibody (APLA) syndrome | 5.89% (n=1) |
| Dermatomyositis                | 5.89% (n=1)             |
| Laboratory abnormalities:      |                         |
| Hypercholesterolemia and hypertriglyceridemia | 23.53% (n=4) |
| Positive ANA (Titer >1:80)     | 17.65% (n=3)            |
| Anti-Ro antibodies             | 5.89% (n=1)             |
| Lupus anticoagulant, anti-cardiolipin, anti-beta-2-glycoprotein-I antibodies | 5.89% (n=1) |
| Hyperhomocysteinemia           | 5.89% (n=1)             |
| Histopathology findings:       |                         |
| Hyaline thrombi within dermal vessels | 94.11% (n=16) |
| Perivascular lymphocytic infiltrates | 76.47% (n=13) |
| Extravasation of RBCs          | 52.94% (n=9)            |
| Fibrinoid degeneration of dermal blood vessels | 35.29% (n=6) |
| Hyalinization of vessel walls in the dermis | 29.41% (n=5) |
| Thickened dermal collagen      | 23.53% (n=4)            |
| Other findings: Neutrophilic infiltrates in chronic ulcerated lesions; atrophic epidermis and sclerosis from lesions of atrophic blanche | 23.53% (n=4) |

Therapeutic profile

Dual antiplatelet therapy (DAPT): Tablet Aspirin 75 mg + Tablet Clopidogrel 150 mg once daily was prescribed to all patients, along with local cleansing with normal saline soaks, leg elevation and cessation of smoking, wherever applicable. All patients were followed up for one year with appropriate clinical and laboratory monitoring. Efficacy of treatment was measured based on Visual Analog Scale (VAS), reduction in ulcer size and Dermatology Life Quality Index (DLQI). VAS <5, ≥50% reduction in ulcer size and DLQI ≤10 was considered as significant improvement. On treatment with DAPT, improvement started within 3-4 weeks and 70.58% (n = 12) patients could achieve significant improvement in 8-12 weeks [Figure 3]. Rest 29.42% (n = 5) patients could not achieve this target in three months of DAPT, in whom tablet pentoxifylline 400 mg thrice daily was added which led to subsequent remission within two months.

Flares were defined as >50% increase in VAS/DLQI/ulcer size from baseline, which was experienced by 11 out of 17 patients. Flare was managed with intramuscular injection of triamcinolone acetonide 40 mg six weekly for a maximum of three doses, or prednisolone 1 mg/kg/day, which was tapered off over 6-8 weeks once the disease activity was controlled. The remaining six patients continued to stay in remission on DAPT ± pentoxifylline.

One patient having hyper-homocysteinemia was co-prescribed folic acid, vitamins B6 and B12 supplements with oral rivaroxaban 20 mg once daily. Patients with SLE and anti-phospholipid antibody syndrome (APLA) were concurrently prescribed hydroxychloroquine. For pain management, tablet paracetamol 650 mg on as-needed basis was given. Those with VAS >6 and extensive ulcers were co-prescribed tablet pregabalin 75 mg once daily. Most patients tolerated the treatment without any adverse
events except for few cases of nausea and gastritis which were managed conservatively.

**Discussion**

LV is designated as an orphan thrombotic disease with reported prevalence of 1:100,000 presenting with painful punched-out ulcers, livedoid changes, retiform/stellate purpura, white atrophic scars and telangiectasias. In our analysis, there was female preponderance and association with obesity, smoking, connective tissue diseases, hyperlipidemia and hyper-homocysteinemia was noticed. Laboratory parameters of thrombophilia were found in two patients. On comparing with a recent study by Criado et al; mean age, clinical presentation and histopathological profile was comparable; thrombophilia markers were present in 66.66% of their cohort in contrast to only 11.76% in our study.

Most patients showed significant improvement in subjective and objective scores with DAPT. A recent systematic review stated that anti-platelet drugs, alone or in combination, are successful in LV. Both aspirin and clopidogrel synergise to target thrombotic pathology in LV. Aspirin, a cyclooxygenase inhibitor, prevents thrombus formation and improves ulcer healing in LV. Clopidogrel irreversibly binds to adenosine diphosphate P2Y12 receptor on surface of platelets, thereby inhibiting activation of glycoprotein Ib/IIa complex which is pivotal for platelet aggregation and activation. It also improves cutaneous microcirculation with evidence of efficacy in management of ulcers of LV. DAPT of aspirin + clopidogrel is a convenient fixed-drug combination, which is readily available, affordable, and effective.

Markers of pathogenesis remain elusive, and the list of laboratory parameters may not be comprehensive. Further research is warranted into the pathogenesis as current schools of thought are divided between thromboembolic and inflammatory pathways. Absence of markers of thrombophilia, resolution of flares with corticosteroids and association with autoimmune connective tissue disorders substantiate the role of autoimmunity in disease orchestration.

Limitations in our study included retrospective design, inability to remove residual confounders/bias and relatively small sample size for deducing statistically significant inferences. More extensive prospective studies with longer follow-ups are necessary.

**Conclusion**

LV is a challenging disease, and more data is needed in Indian context. This cohort aims to contribute to the existing literature pool and provide practical evidence that DAPT can significantly improve disease activity and quality of life.

**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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Nil.

**Conflicts of interest**

There are no conflicts of interest.

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| Age/Sex | Disease duration (years) | Clinical findings | Laboratory abnormalities | Histopathological findings | Associated conditions | Treatment given |
|---------|--------------------------|-------------------|-------------------------|---------------------------|-----------------------|------------------|
| 26/F    | 5                        | Burning pain      | ANA 1:320, anti-Ro positive | Hyaline thrombi in vessels, perivascular lymphocytic infiltration, hyalised vessel walls, fibrinoid necrosis, extravasation of RBCs | SLE                   | DAPT, HCQ        |
| 45/M    | 8                        | Burning pain      | -                        | Hyaline thrombi in vessels, perivascular lymphocytic infiltration, fibrinoid necrosis, extravasation of RBCs | Hypertension          | DAPT + Pentoxifylline |
| 31/F    | 10                       | Atrophie blanche  | -                        | Hyaline thrombi in vessels, perivascular lymphocytic infiltration | -                     | DAPT             |
| 18/F    | 2                        | Atrophie blanche  | ANA 1:160, Anti-La positive | Hyaline thrombi in vessels, thickened collagen | SLE + APLA           | DAPT, HCQ        |
| 23/F    | 2                        | Atrophie blanche  | -                        | -                          | -                     | DAPT             |
| 45/M    | 3                        | Burning pain      | Elevated cholesterol, TG | Epidermal atrophy, thickened collagen, hyalised vessel walls, sclerosis | Obesity, Smoking      | DAPT + Pentoxifylline |
| 19/M    | 2                        | Atrophie blanche  | Hyperhomocysteinemia    | Hyaline thrombi in vessels, perivascular neutrophilic and lymphocytic infiltration, thickened collagen, hyalised vessel walls, fibrinoid necrosis, extravasation of RBCs | -                     | DAPT, rivaroxaban, folica acid, vitamin B6 and B12 |
| 30/F    | 6                        | Burning pain      | Elevated cholesterol, TG | Hyaline thrombi in vessels, perivascular lymphocytic infiltration, fibrinoid necrosis, extravasation of RBCs | Obesity               | DAPT + Pentoxifylline |
| 24/F    | 7                        | Burning pain      | -                        | Hyaline thrombi in vessels, perivascular lymphocytic infiltration | Obesity               | DAPT + Pentoxifylline |
| 44/M    | 1                        | Atrophie blanche  | -                        | Epidermal atrophy, hyaline thrombi in vessels, perivascular lymphocytic infiltration, extravasation of RBCs, sclerosis | -                     | DAPT             |
| 58/F    | 3                        | Atrophie blanche  | ANA 1:160, Elevated cholesterol, TG | Hyaline thrombi in vessels, perivascular lymphocytic infiltration | Obesity, Dermatomyositis | DAPT             |
| 50/F    | 4                        | Atrophie blanche  | -                        | Hyaline thrombi in vessels, perivascular lymphocytic infiltration, fibrinoid necrosis, extravasation of RBCs | -                     | DAPT + Pentoxifylline |
| 43/F    | 2                        | Atrophie blanche  | -                        | Epidermal atrophy, hyaline thrombi in vessels, thickened collagen, hyalised vessel walls, sclerosis | -                     | DAPT             |
| Age/Sex | Disease duration (years) | Clinical findings | Laboratory abnormalities | Histo-pathological findings | Associated conditions | Treatment given |
|---------|-------------------------|-------------------|-------------------------|---------------------------|-----------------------|-----------------|
| 41/M    | 1                       | Burning pain      | -                       | Hyaline thrombi in vessels, perivascular lymphocytic infiltration | Smoking              | DAPT            |
|         |                         | Atrophie blanche  |                         |                           |                       |                 |
|         |                         | Retiform ulcer    |                         |                           |                       |                 |
| 54/M    | 3                       | Burning pain      | Elevated cholesterol, TG | Hyaline thrombi in vessels, extravasation of RBCs | -                     | DAPT            |
|         |                         | Atrophie blanche  |                         |                           |                       |                 |
|         |                         | Retiform ulcer    |                         |                           |                       |                 |
|         |                         | Livedoid changes  |                         |                           |                       |                 |
| 28/F    | 4                       | Burning pain      | -                       | Hyaline thrombi in vessels, perivascular lymphocytic infiltration | -                     | DAPT            |
|         |                         | Atrophie blanche  |                         |                           |                       |                 |
|         |                         | Retiform ulcer    |                         |                           |                       |                 |
| 35/F    | 1                       | Burning pain      | -                       | Hyaline thrombi in vessels, perivascular neutrophilic and lymphocytic infiltration, extravasation of RBCs | -                     | DAPT            |
|         |                         | Atrophie blanche  |                         |                           |                       |                 |
|         |                         | Retiform ulcer    |                         |                           |                       |                 |

M=Male, F=Female, ANA=Anti-nuclear antibody, APLA=Anti-phospholipid antibody, TG=triglyceride, DAPT=Dual anti-platelet therapy, SLE=Systemic lupus erythematosus, HCQ=Hydroxychloroquine, RBCs=Red blood cells