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 atrophie 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 atrophie 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: *Atrophie blanche, hyalinizing vasculopathy, livedoid vasculopathy*

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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 atrophie 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 atrophie blanche	23.53% (*n*=4)

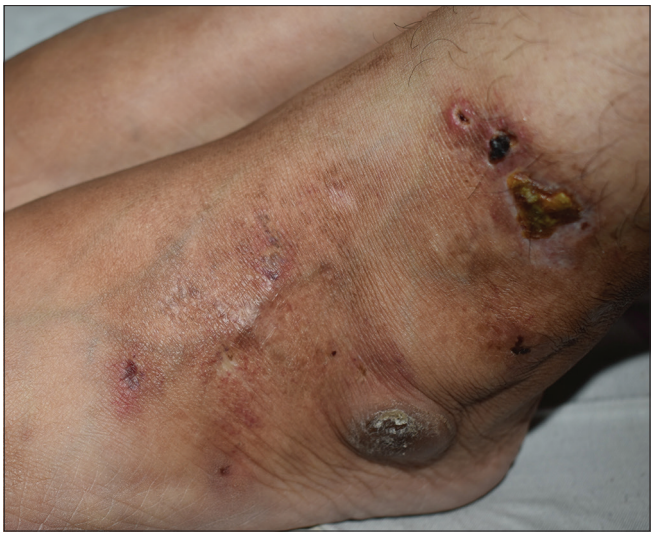

Figure 1: Few punched-out ulcers, stellate purpuric macules with telangiectasias and atrophic scarring around lateral malleoli

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

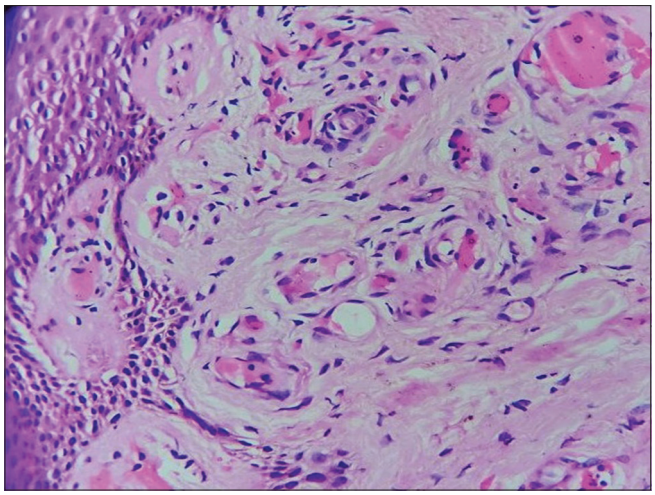

Figure 2: Hyaline thrombi within dermal vessels, perivascular lymphocytic infiltration and thickened dermal collagen (H & E 40x)

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.[4] 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*.[5]; 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.[6] Both aspirin and clopidogrel synergise to target thrombotic pathology in LV. Aspirin, a cyclooxygenase inhibitor, prevents thrombus formation and improves ulcer healing in LV.[7] Clopidogrel irreversibly binds to adenosine diphosphate P2Y12 receptor on surface of platelets, thereby inhibiting activation of glycoprotein IIb/IIIa complex which is pivotal for platelet aggregation and activation.[7] It also improves cutaneous microcirculation with evidence of efficacy in management of ulcers of LV.[3] 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.[8] 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.

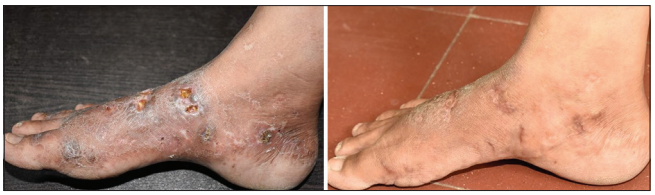

Figure 3: Significant improvement in a 41-year-old male patient with three months of dual anti-platelet therapy

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.

References

1. Vasudevan B, Neema S, Verma R. Livedoid vasculopathy: A review of pathogenesis and principles of management. Indian J Dermatol Venereol Leprol 2016;82:478-88.
2. Lee SS, Ang P, Tan SH. Clinical profile and treatment outcome of livedoid vasculitis: A case series. Ann Acad Med Singap 2003;32:835-9.
3. Kunzler E, Chong BF. Ulcerative livedoid vasculopathy responding to clopidogrel. JAAD Case Rep 2018;4:203-5.
4. Goerge T. Livedoid vasculopathy. Pathogenesis, diagnosis and treatment of cutaneous infarction. Hautarzt 2011;62:627-34; quiz 635.
5. Criado PR, Pagliari C, Morita TCAB, Marques GF, Pincelli TPH, Valente NYS, *et al*. Livedoid vasculopathy in 75 Brazilian patients in a single-center institution: Clinical, histopathological

and therapy evaluation. Dermatol Ther 2021;34:e14810. doi: 10.1111/dth.14810.
6. Micieli R, Alavi A. Treatment for livedoid vasculopathy: A systematic review. JAMA Dermatol 2018;154:193-202.
7. Bilgic A, Ozcobanoglu S, Bozca BC, Alpsoy E. Livedoid vasculopathy: A multidisciplinary clinical approach to diagnosis and management. Int J Womens Dermatol 2021;7:588-99.
8. Khenifer S, Thomas L, Balme B, Dalle S. Livedoid vasculopathy: Thrombotic or inflammatory disease? Clin Exp Dermatol 2010;35:693-8.

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

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

Contd...

Supplemental Table 1: Contd...

Age/ Sex	Disease duration (years)	Clinical findings	Laboratory abnormalities	Histo-pathological findings	Associated conditions	Treatment given
41/M	1	Burning pain Atrophie blanche Retiform ulcer	-	Hyaline thrombi in vessels, perivascular lymphocytic infiltration	Smoking	DAPT
54/M	3	Burning pain Atrophie blanche Retiform ulcer Livedoid changes	Elevated cholesterol, TG	Hyaline thrombi in vessels, extravasation of RBCs	-	DAPT
28/F	4	Burning pain Atrophie blanche Retiform ulcer	-	Hyaline thrombi in vessels, perivascular lymphocytic infiltration	-	DAPT
35/F	1	Burning pain Atrophie blanche Retiform ulcer	-	Hyaline thrombi in vessels, perivascular neutrophilic and lymphocytic infiltration, extravasation of RBCs	-	DAPT

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