

A Ten-Year Retrospective Study on Livedo Vasculopathy in Asian Patients

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Abstract

Introduction: This study aims to analyse the clinico-epidemiological characteristics of Asian patients diagnosed with livedo vasculopathy (LV). **Materials and Methods:** We performed a retrospective analysis of all patients diagnosed with LV from 1997 to 2007 at our centre. **Results:** Seventy patients were diagnosed with LV with a mean age of 39 years, female: male ratio of 3:1 and no racial predilection. Most cases remained purely cutaneous, presenting with painful leg ulcers and atrophie blanche. Peripheral neuropathy was the only extra-cutaneous complication (9%). In patients who were screened, associations included hepatitis B (7%) and hepatitis C (4%), positive anti-nuclear antibody (14%), positive anti-myeloperoxidase antibody (5%), positive anti-cardiolipin antibodies (7%) and positive lupus anticoagulant (2%). In 49 patients who achieved remission, 55% required combination therapy, most commonly with colchicine, pentoxifylline and prednisolone. In those treated successfully with monotherapy, colchicine was effective in 59% followed by prednisolone (17.5%), pentoxifylline (17.5%) and aspirin (6%). Mean follow-up period was 50 months. **Conclusion:** LV in Asian patients is a high morbidity, chronic relapsing ulcerative skin condition. Most patients require induction combination therapy for remission. As further evidence emerges to support a procoagulant pathogenesis, a standardised protocol is needed to investigate for prothrombotic disorders during diagnosis.

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Introduction

Livedo vasculopathy (LV), previously referred to as livedo vasculitis or atrophie blanche, is a chronic, recurrent disease, which was first described by Feldaker et al¹ in 1955 as “livedo reticularis with summer ulcerations”. It usually presents as recurrent, painful, deep punched-out ulcers on the lower extremities, which heal with stellate, porcelain-white scars, known as atrophie blanche. Net-like reticulated erythema, such as livedo racemosa or livedo reticularis, is often also associated with LV. The exact aetiology of LV still remains unknown although the disease is now widely believed to likely have a procoagulant pathogenesis.² This retrospective study aims to analyse the demographics, comorbidities, clinicopathological features, laboratory findings and treatment outcomes of LV patients seen over a 10-year period at a tertiary dermatology referral centre, in order to further understand the clinico-epidemiological features of this disease in Asians and to refine our treatment strategies based on documented clinical outcomes.

Materials and Methods

All patients with diagnoses of ‘vasculitis’, ‘livedo vasculopathy’, ‘livedo vasculitis’, ‘atrophie blanche’, and/or ‘livedo reticularis’ from January 1997 to December 2007, were identified from our clinical and histological databases. Their case records were reviewed and only patients with a diagnosis of LV were included. The diagnosis of LV was based on the following established clinical and histological criteria.^{3,4} Clinical criteria included painful purpuric macules, typically on the lower extremities, that ulcerated and then slowly healed with atrophic stellate scars and surrounding telangiectasia.³ Histological criteria included segmental hyalinisation, endothelial proliferation, fibrin deposition, dermal vessel thrombosis, with minimal or absent perivascular lymphocytic infiltrate and leucocytoclasia typically seen in a vasculitis.⁴ Exclusion criteria included equivocal cases of vasculitis, cases where another cause for ulceration had already been elucidated, for example, cutaneous polyarteritis nodosa (PAN), and

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cases with incomplete documentation. Retrospective chart reviews were performed on all LV patients to obtain details on epidemiology, clinical characteristics, treatment and outcome. Approval had been obtained from the national research ethics board prior to study commencement.

Results

A total of 1070 patients were identified under the master index diagnoses of 'vasculitis', 'livedo vasculopathy', 'livedo vasculitis', 'atrophie blanche', and/or 'livedo reticularis'. After careful chart review, only 70 patients met the inclusion criteria and were diagnosed with LV based on clinicopathological correlation.

Demographics

There was female predominance (76%) with a mean age at presentation of (39 ± 15) years (range, 15 to 75). Table 1 summarises the key demographic features of the patients.

Table 1. Demographic Characteristics of the 70 Livedo Vasculopathy Patients

Characteristics	Number of Patients (%)
Age at diagnosis (years)	
<20	8 (11)
21 to 40	33 (47)
41 to 60	21 (33)
>60	8 (11)
Ethnicity	
Chinese	51 (73)
Malay	8 (11)
Indian	7 (10)
Others	4 (6)
Gender	
Female	53 (76)
Male	17 (24)

Clinical and Histological Features

Most patients (70%, $n = 49$) presented with multiple active, painful, necrotising ulcers on both lower limbs (Figs. 1, 2). The rest had healed ulcers or evidence of previous ulcers in the form of scarring. The key presenting clinical features are summarised in Table 2. Histology reports of 63 patients (90%) were reviewed and the key findings were dermal vessel thrombosis (57%), fibrin deposition (38%), endothelial proliferation (14%) and segmental hyalinisation (13%) (Figs. 3, 4). Out of 55 patients for whom direct immunofluorescence testing was performed, all but 1 patient (98%) had findings consistent with vasculitis.



Fig. 1. A deep punched-out ulcer with dusky inflamed edges, surrounding purpura, telangiectasia and porcelain-white atrophie blanche scars.



Fig. 2. Multiple necrotic ulcers around the ankles of a patient. Note the healed atrophie blanche scars and surrounding dusky net-like reticulated erythema suggestive of livedo racemosa.

Table 2. Key Presenting Clinical Features of the 70 Livedo Vasculopathy Patients

Clinical Features	Number of patients (%)
Active Ulcers – Number*	
Single	10 (14)
Multiple	39 (56)
Active Ulcers – Location*	
Upper limb	1 (1)
Lower limb	48 (69)
Atrophie blanche/ scars	46 (66)
Livedo reticularis	17 (24)
Deep Infection e.g. cellulitis	3 (4)

*Forty-nine of 70 patients had active ulcers on presentation. The rest of the patients had healed ulcers or evidence of previous ulcers in the form of scarring.

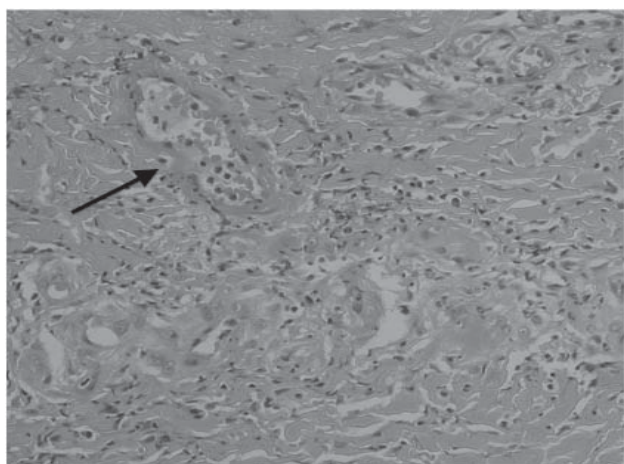


Fig. 3. Fibrin exudation around an upper dermal blood vessel (arrow). Note proliferation of upper dermal blood vessels lined by plump endothelial cells, representing areas of neovascularisation. (Haematoxylin and eosin, original magnification $\times 20$).

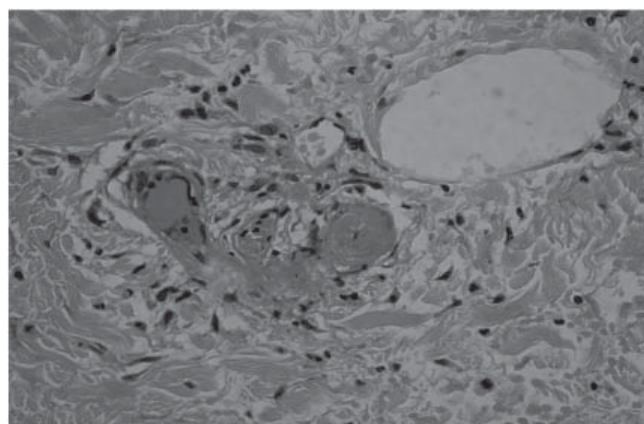


Fig. 4. Fibrin thrombi obliterating the lumina of dermal blood vessels with surrounding pauci-inflammatory infiltrate. (Haematoxylin and eosin, original magnification $\times 40$).

Comorbidities and Manifestations

Extra-cutaneous involvement occurred in 9% ($n = 6$) of patients with the vast majority, 91%, having disease confined to the skin. These 6 patients presented with neurological symptoms of numbness and paraesthesia on their affected legs. Abnormal clinical neurological examination and nerve conduction studies confirmed the diagnosis of peripheral neuropathy in all 6 patients.

With regard to immunological testing, 91% ($n = 64$) were screened for anti-nuclear antibody (ANA) and 14% ($n = 9$) tested positive. However, none of the 13 patients who were tested for anti-double stranded DNA antibody (anti-dsDNA) had positive results and only 2 out of 40 patients (5%) were positive for anti-myeloperoxidase antibody. Two patients had pre-existing connective tissue disease—one had systemic lupus erythematosus, which

had been diagnosed 2 years prior to LV and the other had rheumatoid arthritis for 8 years before developing LV. Of note, one patient was concurrently diagnosed with mixed cryoglobulinaemia according to the Brouet Classification. This patient was co-managed with the rheumatologists and responded well to oral prednisolone 0.5 mg/kg/day, with remission achieved 11 months after initiation of therapy.

As part of the thrombophilia investigations, antiphospholipid antibody testing was carried out in 45 patients (64%). Three patients (7%) had positive anti-cardiolipin antibodies (ACA Immunoglobulin G and Immunoglobulin M) and 1 patient (2%) was positive for lupus anticoagulant (LAC). However, only 2 patients fulfilled sufficient criteria for the antiphospholipid syndrome (APS), based on the established international consensus criteria for APS.⁵

There were 6 patients with signs and symptoms suggestive of chronic venous disorders such as dependent leg edema with varicosities, stasis dermatitis, and lipodermatosclerosis and they were further evaluated with lower limb venous duplex studies. Four out of these 6 patients had evidence of venous insufficiency and incompetence on venous duplex examination.

Viral hepatitis B was screened for in 28 patients (40%) and 2 (7%) tested positive. Twenty-five patients (35%) were screened for hepatitis C and only 1 patient (4%) was tested positive.

Treatment and Outcome

Treatment of LV comprised monotherapy or combination treatment with one or more of the following oral agents: prednisolone 0.5 mg/kg/day, colchicine 1 mg/day, pentoxifylline 800 to 1200 mg/day, aspirin 100 mg/day, cyclophosphamide 1.5 to 2.5 mg/kg/day, azathioprine 2 to 3 mg/kg/day, dapsone 50 to 100 mg/day and hydroxychloroquine up to 6.5 mg/kg/day.

Remission was defined as absence of new lesions for at least 2 months, whilst on stable maintenance immunosuppressive therapy. The mean time to remission was 9 months (range, 0.5 to 60 months).

In the 49 patients who achieved first remission, 55% ($n = 27$) required combination therapy, most commonly with prednisolone, pentoxifylline and colchicine. In those treated successfully with monotherapy (35%, $n = 17$), colchicine was used in 59% ($n = 10$) followed by prednisolone (17.5%, $n = 3$), pentoxifylline (17.5%, $n = 3$) and aspirin (6%, $n = 1$). Five patients (10%) recovered with topical corticosteroids and judicious wound care.

With regard to combination therapy leading to first remission, the top 3 combinations were prednisolone,

colchicine and pentoxifylline (26%, $n = 7$) followed by prednisolone and azathioprine (15%, $n = 4$) and lastly prednisolone and colchicine (11%, $n = 3$).

Out of the 49 patients with documented remission, 59% ($n = 29$) suffered at least one relapse over a mean follow-up period of 50 months. Some patients suffered as many as 7 relapses while others had none, giving a mean of 1.7 relapses. Twenty patients were lost to follow-up before any documented remission and only 1 patient had active disease throughout the duration of the study.

Discussion

We report on a large series of Asian patients with LV. Majority of our patients (76%) were in their third or fourth decade of life and female, consistent with previous reports of a female predominance in both Asian⁶ and Western cohorts.⁷ Although, the degree of female predominance is less marked compared to the Singapore lupus cohort, which reported a 92.4% proportion of females,⁸ we believe that the higher prevalence of autoimmune diseases in females⁹ may account in part for the female predominance in LV. In both cohorts, there was no particular racial predilection, with the distribution similar to the national racial demographics.

We have summarised the key findings of our cases compared with other Asian and Western case series in Table 3. Of note, our study found that only a small minority of LV cases were associated with connective tissue disease (3%), chronic venous insufficiency (6%) and thrombophilic conditions. In contrast, a similar retrospective study of a large Western cohort of 45 LV patients seen at Mayo Clinic, Rochester, USA, found a higher prevalence of connective tissue disease (13%), chronic venous insufficiency (9%), positive ACA (29%) and positive LAC (18%).² This lack of significant consistent association with any particular disease or autoantibody in both the Asian and Western cohorts suggests that LV may be a distinct dermatological condition with no firm link to other medical conditions.

Comparing the younger patients (less than or equal to 40 years old) with the older patients in our series, there was a higher prevalence of chronic venous insufficiency in the older age group (3 out of 4 patients) whereas a higher prevalence of connective tissue disease (2 out of 3 patients) and of neurological involvement (4 out of 6 patients) in the younger group. It however remains difficult to assess the significance of these differences, in view of the small numbers of patients in each subgroup. None of the patients had a positive family history of LV.

The most consistent clinical feature in our patients was the presence of multiple necrotic painful ulcers on the lower limb, especially around the gaiter area (Table 2). Important differential diagnoses for painful leg ulceration

and reticulated erythema should however be excluded before making a diagnosis of LV. This includes small and medium vessel vasculitis such as cutaneous polyarteritis nodosa (PAN), cryoglobulinemia, microscopic polyarteritis, collagen disease-associated vasculitis, APS, chronic venous insufficiency and pyoderma gangrenosum.

Cutaneous PAN, in particular, is one of the conditions that closely resembles LV. Clinically, it presents with deep vasculitic ulcers and livedo reticularis, just like in LV, but in addition, there are typically tender subcutaneous nodules, a feature that was not seen in our LV patients. Cutaneous PAN is also associated with a higher prevalence of anti-myeloperoxidase antibodies and anti-phosphatidylserine-prothrombin complex (anti-PS/PT) antibodies, which can be detected on laboratory testing,¹⁷ again reiterating the need for careful clinicopathological correlation when evaluating all cases of ulceronecrotic vasculitis.

Numerous reports have recently emerged supporting a thrombotic pathogenesis for LV since it has been associated with the antiphospholipid syndrome,¹⁵ protein C deficiency,¹⁸ hyperhomocysteinemia¹⁹ and gene polymorphisms linked with altered procoagulant mechanisms including that of factor V Leiden,²⁰ prothrombin (PRT; G20210A),²¹ methylenetetrahydrofolate reductase (MTHFR; C677T)¹⁹ and the plasminogen activator inhibitor (PAI)-1 4G/5G insertion-deletion.²² Unfortunately, we could not corroborate these findings as tests for gene polymorphisms, homocysteine levels or protein C and S were not performed in the majority of our patients.

Neurological involvement was documented in 9% of our patients, all with peripheral neuropathy. This has been reported previously in the literature. Winkelmann et al²³ first reported an LV patient who had mononeuropathy multiplex and in a separate case series of 21 patients, 2 (10%) had sensory changes, although no electrophysiological testing or nerve biopsies were done.²⁴ It has been hypothesised that neuropathy occurring in LV may be secondary to ischaemia from vascular thrombosis of vasa nervorum.²⁵ In our study, no significant risk factors could successfully predict neurological involvement. Consideration should be given to nerve biopsies in future to further delineate the pathogenesis behind neurological involvement.

Treatment of this condition continues to pose a challenge to dermatologists. In our study, induction combination therapy was more successful than monotherapy in achieving clinical remission. This could suggest that combination therapy be considered as first-line treatment, especially for severe disabling disease. Lee et al²⁶ similarly demonstrated that a combination of aspirin and pentoxifylline yielded better results compared to either drug alone. Other studies and reports have shown varied effectiveness of a range of medications including antithrombotic agents

Table 3. Comparison of Various Asian and Western Series of Livedo Vasculopathy

	Country	Western (W) or Asian (A)	Number of Patients	Mean Age at Diagnosis (years)	Female: Male	Clinical Features	History of Connective Tissue Disease	ANA, Other Auto-antibodies	Coagulation Profile	Treatment
Gan EY et al	Singapore	A	70	39	3:1	Painful ulcers, atrophie blanche	2 (systemic lupus erythematosus, rheumatoid arthritis)	ANA + (9/64), Anti-myeloperoxidase + (2/40)	ACA + (3/45), LAC + (1/45), 2 patients fulfilled criteria for antiphospholipid syndrome	Prednisolone + pentoxifylline + colchicine (commonest successful combination)
Lee JH et al ¹⁰	South Korea	A	8	23	5:3	Painful ulcers, atrophie blanche	-	All ANA negative	-	PUVA
Tsai TF et al ⁶	Taiwan	A	56	30	19:9	Painful ulcers	-	-	-	-
Hsiao GH et al ¹¹	Taiwan	A	2	36	2:0	Painful ulcers	-	-	-	Danazol 200mg/day
Yamamoto M et al ¹²	Japan	A	2	33	2:0	Painful ulcers, atrophic scars	-	ANA, anti-dsDNA negative (1); Anti-dsDNA, cryoglobulin negative (1)	Normal	Aspirin + Dipyridamole (1); Ticlopidine + Dipyridamole (1)
Sauer GC ¹³	USA	W	6	56	1:2	Painful ulcers, atrophie blanche	-	-	-	Pentoxifylline
Sams WM ¹⁴	USA	W	8	53	5:3	Painful ulcers	Nil	All ANA negative	-	Pentoxifylline ± aspirin and dipyridamole
Papi M et al ⁷	Italy	W	8	33	5:3	Ulcers, atrophie blanche	-	ANA + (1),	ACA IgG + (1)	-
Hairston BR et al ²	USA	W	45	45	32:13	Ulcers (68.9%), Atrophie blanche (71.1%)	6 (13% - rheumatoid arthritis, scleroderma, MCTD, UCTD)	-	ACA + (28.6%), LAC + (17.9%), Factor V Leiden + (2/9), Decreased protein C and S (2/15)	-
Acland KM et al ¹⁵	UK	W	4	27	1:1	Ulcers	-	Negative for other autoantibodies	All ACA +	Aspirin (2); Dapsone (1); Prednisolone + danazol (1)
Drucker CR et al ¹⁶	USA	W	7	41	5:2	Painful ulcers	-	-	All with platelet function abnormalities	Aspirin + Dipyridamole

ACA: anti-cardiolipin antibody; anti-dsDNA: anti-double stranded DNA; ANA: anti-nuclear antibody; LAC: lupus anticoagulant; MCTD: mixed connective tissue disease; UCTD: undifferentiated connective tissue disease; PUVA: psoralen and ultraviolet A light

like pentoxifylline,¹⁴ antiplatelets,^{12,27} anticoagulants like warfarin and heparin,²⁸⁻³⁰ corticosteroids,³¹ anabolic steroids like danazol,¹¹ intravenous immunoglobulin³² and newer agents such as rituximab³³ or even psoralen and ultraviolet A light (PUVA) therapy.¹⁰

The treatment combination with best remission rates in our study comprised prednisolone, pentoxifylline and colchicine, 3 drugs with different mechanisms of action. Prednisolone is a corticosteroid with potent anti-inflammatory effects. Pentoxifylline, on the other hand,

is a vasoactive drug which improves microcirculatory blood flow by increasing erythrocyte flexibility and significantly reducing blood viscosity,¹⁴ thereby enhancing peripheral tissue oxygenation. Colchicine, which has not been described previously in the treatment of LV, has anti-inflammatory effects via neutrophil inhibition. Since these drugs are synergistic, it suggests that both thrombosis and inflammation may play important roles in the complex pathogenesis of this disease, although the exact contribution of each remains unknown.

Although the types of wound dressings were not specifically investigated in our study, we observed that good wound bed preparation and pain management formed a crucial aspect of disease management, in addition to systemic therapy. Newer antiseptic dressings such as silver-based dressings and iodine based ointments, such as Iodosorb (Smith and Nephew, UK), were particularly useful for antimicrobial control in these chronic wounds typically colonised by polymicrobial, multi-resistant flora. Regular wound debridement was also needed as necrotic slough often re-accumulated on the wound bed during active disease. Proactive prescription of strong analgesics helped to reduce morbidity in these patients, who often had significant inflammatory wound pain.

As a retrospective review, our study has several limitations, mainly related to study design, data collection and capture. Without a standardised protocol of investigations, comprehensive screening of comorbidities was not performed for every patient, particularly for underlying prothrombotic disorders. Accuracy of data collection also relied on adequate documentation in the medical records. Despite the above limitations, we believe that several clinically useful conclusions can be drawn from the study.

Conclusion

In summary, combination therapy should be considered when managing LV patients, in particular the use of oral corticosteroid, colchicine and pentoxifylline, which showed to be most effective. Managing physicians should always remain vigilant for extra-cutaneous manifestations, and patients presenting with persistent or progressive numbness, neuralgia or weakness of the limbs should be promptly referred for formal neurological assessment. Lastly, a standardised protocol should be established to ensure the accurate diagnosis of LV and its associated predisposing factors or diseases including prothrombotic disorders. Larger prospective studies will be useful to further understand the disease including establishing the best treatment regimens and investigation protocols.

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