

Co-occurring livedoid vasculopathy and limited cutaneous systemic sclerosis associated gangrene successfully managed with alprostadil and aspirin

Dear Editor,

Livedoid vasculopathy is a rare vascular thrombosing disorder that presents with recurrent painful ulceration on the distal lower extremities. The association of livedoid vasculopathy with systemic sclerosis is exceedingly uncommon.¹ Prostaglandin analogues, commonly used for the treatment of digital ulcers in systemic sclerosis, have been found effective for ulcers of livedoid vasculopathy in a few case reports. We report a case of systemic sclerosis-associated digital gangrene and livedoid vasculopathy with a favourable response to alprostadil, a prostaglandin E-1 agonist.

A 43-year-old man presented with a one-year history of Raynaud’s phenomenon, sclerodactyly, digital tip ulcers and pitted scars. There was binding down of skin over the hands, feet, face and neck. There were a few mat-like telangiectasias on the cheeks. The modified Rodnan skin score was 10. He also had multiple, small, well-defined ulcers with irregular borders, more prominent on the left medial malleolus, for the past six months. There were geometrical porcelain white scars with peripheral hyperpigmentation and telangiectasias, more prominent on the right medial malleolus [Figure 1]. There was painless, blackish discoloration over the distal part of the second toe of the right foot. The peripheral pulses were palpable. The patient complained of on-and-off pus discharge from ulcers and a continuous dull aching pain at the site of ulceration, which was exacerbated by touch and warm weather. There was no history of smoking, intermittent claudication, rest pain, or significant systemic symptoms.

The complete hemogram, liver and renal biochemistries and coagulation profile (prothrombin time, activated partial thromboplastin time, INR) were within the normal limits. Anti-nuclear antibodies (3+ intensity; nuclear speckled pattern on indirect immunofluorescence) and anti-topoisomerase antibodies (2+) were positive. The work-up for hypercoagulable states, including protein C, protein S,



Figure 1: Multiple well-defined ulcers with irregular borders on the medial malleolar region with adherent yellowish-brown crusting on the surface.

anti-thrombin III, homocysteine, lupus anticoagulant and serum protein electrophoresis, were within the normal limits. The computed tomography (CT) chest showed limited bilateral symmetrical peripheral intralobular septal thickening with patchy ground glass opacities suggestive of interstitial lung disease. Echocardiogram, barium swallow,

How to cite this article: Baskaran N, Mustari A, Malhi K, Bishnoi A, De D, Handa S, *et al.* Co-occurring livedoid vasculopathy and limited cutaneous systemic sclerosis associated gangrene successfully managed with alprostadil and aspirin. *Indian J Dermatol Venereol Leprol.* doi: 10.25259/IJDVL_89_2024

Received: January, 2024 **Accepted:** April, 2024 **Epub Ahead of Print:** June, 2024

DOI: 10.25259/IJDVL_89_2024

This is an open-access article distributed under the terms of the Creative Commons Attribution-Non Commercial-Share Alike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.

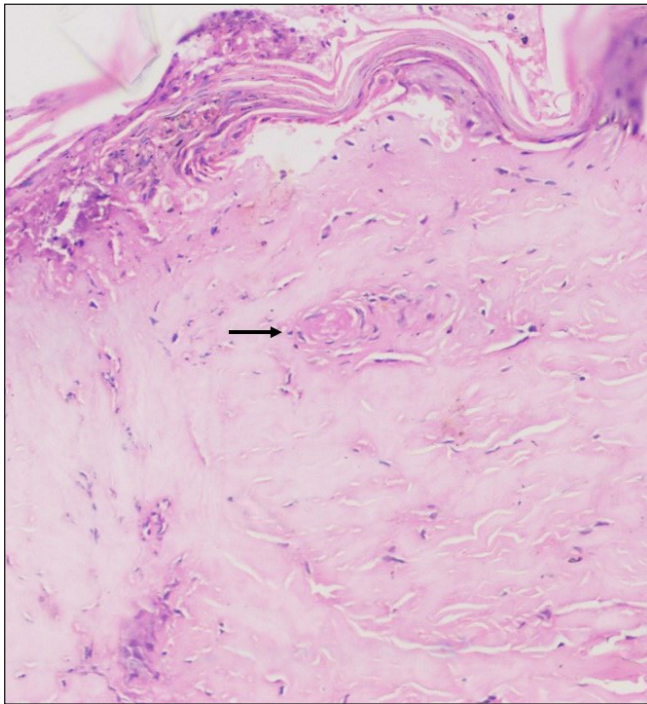


Figure 2: Fibrin thrombi (black arrow) occluding the lumen of small vessels in the dermis with mild inflammatory infiltrate in the perivascular location (Haematoxylin and eosin, 200x).

24-hour urine protein and pulmonary function tests were normal. Ultrasound Doppler of the arterial and venous systems of both lower limbs demonstrated normal triphasic flow in vessels with no obvious abnormality. Skin biopsy from the ulcer margin showed fibrin thrombi occluding the lumen of small vessels in the upper and lower dermis, with a mild inflammatory infiltrate in the perivascular location consistent with livedoid vasculopathy [Figure 2].

The patient fulfilled the American College of Rheumatology-European League Against Rheumatism (ACR-EULAR) classification criteria for systemic sclerosis. A final diagnosis of limited cutaneous systemic sclerosis with livedoid vasculopathy and digital gangrene was reached. The patient was treated with nifedipine 20 mg/day and aspirin 75 mg/day. In view of digital gangrene, alprostadil 250 µg intravenously was administered over five days along with cold protection. Pain reduced a month after the first cycle of infusions, and the ankle ulcers started healing after that. A total of three cycles of alprostadil were administered at monthly intervals. Complete healing of ulcers with stellate scars occurred after the third cycle of alprostadil [Figure 3]. Due to the persistence of the ulcers for six months prior to treatment, the immediate symptomatic relief in pain after the first cycle of alprostadil and the complete healing of ulcers after subsequent cycles; the improvement was attributed to alprostadil. Raynaud's phenomenon was well-controlled and gangrene of the toe also recovered. The patient has been under follow-up for 12 months after the last cycle of alprostadil and has experienced no further recurrence of ulcers.



Figure 3: Complete healing of ulcers with stellate scars (black arrow) post-treatment.

Livedoid vasculopathy is a vascular hyalinising disorder characterised by the thrombosis of vessels.² Hypercoagulability forms the cornerstone of the pathogenesis, leading to thrombosis of vessels, occlusion of cutaneous microvasculature and, subsequent ulceration of the skin. The ulcers have a predilection for the lower extremities, are characteristically small, irregular and painful and heal with classical porcelain white stellate scars termed atrophic blanche.

Vasculopathy plays an important role in the pathogenesis of systemic sclerosis. There is vascular occlusion and fibrosis due to interactions between the endothelial cells, smooth muscle cells, extracellular matrix, and mediators like endothelin. In a retrospective series by Furtado *et al.*, at least one microvascular complication was present in 50.5% of cases with systemic sclerosis. They also found elevated D-dimer levels in 43.5% of cases and proposed it to be the cause of microvascular and macrovascular complications.³ The ulcers and gangrene associated with systemic sclerosis are more common on the fingers, though the involvement of the toes can occur. However, the association of livedoid vasculopathy with systemic sclerosis is rare.¹ The presence of irregular, painful ulcers over the feet with atrophic blanche in a case of systemic sclerosis should raise the possibility of livedoid vasculopathy. A search for vascular complications, including pulmonary artery hypertension and renal crisis, should be done in such patients.³ A biopsy from the edge of the ulcer would help in establishing the diagnosis. Investigations to identify other inherited and acquired causes of thrombophilia, which would include protein C, protein S, anti-thrombin III, homocysteine and anti-phospholipid antibodies, should be performed. Management should target the vasculopathy in addition to the standard treatment of systemic sclerosis.

Various treatment modalities for livedoid vasculopathy act by correcting coagulation abnormalities and/or controlling inflammation. Drugs acting via the coagulation pathway

1 include anticoagulants like rivaroxaban and dabigatran,
2 antiplatelet drugs like aspirin and fibrinolytics. Anti-
3 inflammatory agents, including corticosteroids and
4 immunosuppressants like azathioprine, cyclosporine,
5 cyclophosphamide and baricitinib are also used in treatment.²

6 Alprostadil is a prostaglandin E1 (PGE1) agonist that causes
7 vasodilatation by increasing cAMP production. In addition,
8 it counteracts the vasoconstrictive effect of leukotriene D4,
9 inhibits platelet aggregation, has cytoprotective properties,
10 enhances fibrinolytic activity, downregulates adhesion
11 proteins like intercellular adhesion molecule 1 and vascular
12 cell adhesion molecule 1 (ICAM-1, VCAM-1) and E-selectin,
13 and upregulates thrombomodulin, ultimately leading to
14 increased vascular flow. Adverse effects with alprostadil
15 are less common and include flushing, alterations in blood
16 pressure and heart rate, headaches, hypokalemia, reflux and
17 flu-like symptoms. The efficacy is comparable for most PGE1
18 agonists, however, alprostadil is associated with a better
19 safety profile, a propensity to prevent new digital ulcers and
20 lower cost.
21

22 There are previous reports of treatment of livedoid
23 vasculopathy with prostanoids, which include four patients
24 with PGE-1, four with beratoprost, three with iloprost and
25 one with alprostadil-alpha.^{4,7} Prostanoid was chosen for
26 treatment in our case owing to its efficacy in both Raynaud's
27 phenomenon and digital ulcers and livedoid vasculopathy.

28 In conclusion, the index case demonstrates a rare
29 co-occurrence of livedoid vasculopathy in a man with
30 limited cutaneous systemic sclerosis treated with alprostadil.
31 Prostaglandin analogues are a promising treatment option
32 for this rare co-occurrence of disorders with underlying
33 vasculopathy.
34

35 Declaration of patient consent

36 The authors certify that they have obtained all appropriate
37 patient consent.
38

39 Financial support and sponsorship

40 Nil.
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56

Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation:

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

Narayanan Baskaran , **Akash Mustari**, **Kittu Malhi**,
Anuradha Bishnoi, **Dipankar De**¹, **Sanjeev Handa**,
Debajyoti Chatterjee², **Rahul Mahajan**¹

Departments of Dermatology, ¹Dermatology, Venereology and Leprology,
²Histopathology, PGIMER, Chandigarh, India

Corresponding author:

Dr. Rahul Mahajan,
Department of Dermatology, Venereology and Leprology
PGIMER, Chandigarh, India.
drrahulpgi@yahoo.com

References

1. Thomas JR, Winkelmann RK. Vascular ulcers in scleroderma. *Arch Dermatol* 1983;119:803–7.
2. 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.
3. Furtado S, Dunogué B, Jourdi G, Chaigne B, Chibah A, Legendre P, *et al.* High D-dimer plasma concentration in systemic sclerosis patients: Prevalence and association with vascular complications. *J Scleroderma Relat Disord* 2021;6:178–86.
4. Kawakami T, Kawasaki K, Mizoguchi M, Soma Y. Therapeutic effect of lipoprostaglandin E1 on livedoid vasculitis associated with essential cryoglobulinaemia. *Br J Dermatol* 2007;157:1051–3.
5. Nonaka Y, Sibue K, Shimizu A, Koga T, Toshitani S. Lipo-prostaglandin E1 therapy for livedo reticularis with ulceration. *Acta Derm Venereol* 1997;77:246–7.
6. Hoogenberg K, Tupker RA, van Essen LH, Smit AJ, Kallenberg CG. Successful treatment of ulcerating livedo reticularis with infusions of prostacyclin. *Br J Dermatol* 1992;127:64–6.
7. Mofarrah R, Aberer W, Aberer E. Treatment of livedoid vasculopathy with alprostadil (PGE-1): Case report and review of published literature. *J Eur Acad Dermatol Venereol* 2013;27:e252–4.