Livedo reticularis: A review of the literature

Vijaya Veeranna Sajjan, Snehal Lunge, Manjunathswamy Basavapuruda Swamy, Ashok Maharudrayya Pandit

Department of Dermatology, Jawaharlal Nehru Medical College, Belgaum, Karnataka, India

ABSTRACT

Livedo reticularis (LR) is a cutaneous physical sign characterized by transient or persistent, blotchy, reddish-blue to purple, net-like cyanotic pattern. LR is a benign disorder affecting mainly middle-aged females, whereas livedo racemosa (LRC) is pathologic, commonly associated with antiphospholipid antibody syndrome. This article aims to review the causes of LR and LRC along with the evaluation and management.

Key words: Antiphospholipid antibody syndrome, livedo racemosa, livedo reticularis

Access this article online

Website: www.idoj.in

DOI: 10.4103/2229-5178.164493

Quick Response Code:

Address for correspondence:
Dr. Vijaya V. Sajjan, Department of Dermatology, JNMC, KLE University, Belgaum - 590 010, Karnataka, India.
E-mail: vijaya_sajjan@yahoo.com

INTRODUCTION

Hebra first used the term livedo more than a century ago, to describe a violet skin discoloration caused by an abnormality of the local blood circulation.[1] Livedo reticularis (LR) is a cutaneous physical sign characterized by transient or persistent, blotchy, reddish-blue to purple, net-like cyanotic pattern. LR is a manifestation of cutaneous blood flow disturbance that may occur in a variety of physiologic and pathologic states. They may be benign, as in physiologic cutis marmorata of infancy, or serious, as in the vasculitis of lupus erythematosus. To understand the spectrum of diseases associated with LR, it is necessary to rationally evaluate patients who present with this distinctive net-like vascular pattern in the skin. This article aims to review the conditions associated with LR and the concepts relating to its pathogenesis.

Ehrmann in 1907 distinguished two different patterns of livedo: The physiological LR and the pathological livedo racemosa (LRC).[2] The livid rings in both forms are caused by reduced blood flow and lowered oxygen tension at the peripheries of the skin segments.[3,4]

Livedo reticularis and livedo racemosa

The distinction between LRC and LR is a newer concept and is not present in most of the older literature. LR is a benign, primary disorder that affects young to middle-aged females. The livid conical discoloration is symmetric, reversible, and uniform [Figure 1]. Although LRC is a secondary disorder, it is pathologic and permanent. The livid conical discoloration is symmetric, irreversible, and "broken" [Figure 2]. Antiphospholipid antibody testing should be obtained in all patients presenting with LRC.[5]

Epidemiology

LRC is the most common dermatologic presentation in patients with antiphospholipid syndrome (APS), presenting in 25% of patients with primary APS and in 70% of patients with SLE-associated APS.[6]

Physiologic microanatomy

To explain the livedo pattern on physiologic grounds, Renault (1883) and later Unna (1896) and Spalteholz (1927)[1,7] postulated that the cutaneous vasculature consists of a series of 1–3 cm cones, with the apex of each cone deep in the dermis at the site of an ascending arteriole. They proposed that at the margins of each cone, the density of the arterial bed is diminished, but the superficial venous plexus is more prominent. More recently, careful clinical

Cite this article as: Sajjan VV, Lunge S, Swamy MB, Pandit AM. Livedo reticularis: A review of the literature. Indian Dermatol Online J 2015;6:315-21.

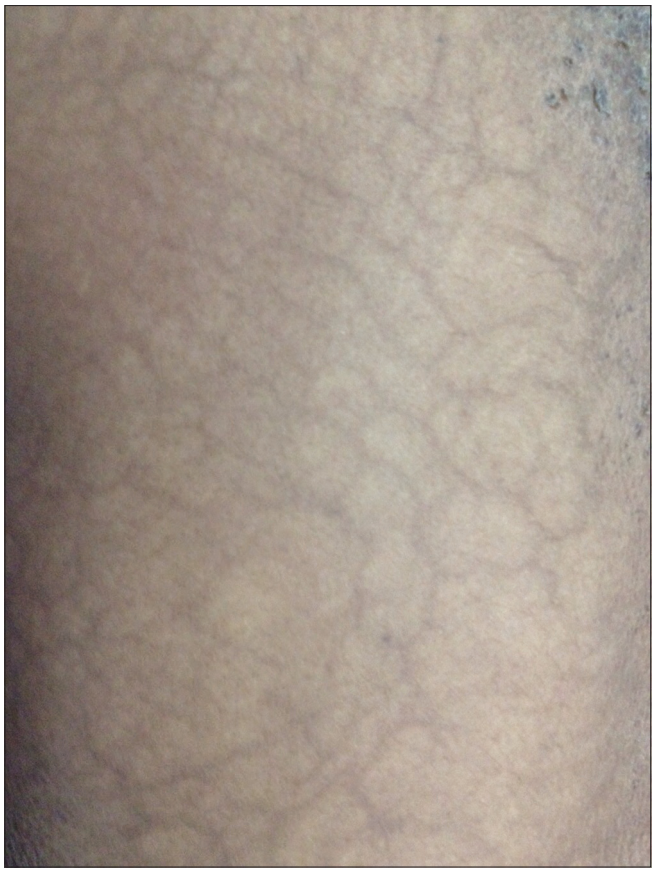


Figure 1: Livedo reticularis

observation,[7] including the use of capillary microscopy and skin temperature recordings,[1] have supported this view of cutaneous vascular microanatomy. Assuming this model, any physiological or pathological process that impedes blood flow to the skin could produce an increased proportion of deoxygenated hemoglobin and thereby resulting in prominent livid coloration in the predominantly venous areas at the margins of the cones. Many processes can result in diminished blood flow and can potentially produce LR. The etiopathogenesis of LR associated with certain diseases such as cutis marmorata telangiectatica congenita (CMTC), hypothyroidism, and the idiopathic varieties of LR is however not clear.

Physiologic arteriolar vasospasm produces reversible cutaneous discoloration of LR. The LR can occur as a physiological response to cold exposure, when it is known as cutis marmorata, or the skin color changes may be unrelated to ambient temperature. Protracted arteriolar vasospasm, thrombosis, and/or hyperviscosity causes the pathologic skin changes of LRC. Venodilatation of the venous plexus may be triggered by hypoxia or autonomic dysfunction.

A role for the endothelial cells has also been suggested in the subset of patients of APS with LRC. The interaction of APL antibodies with endothelial cells could induce LRC and

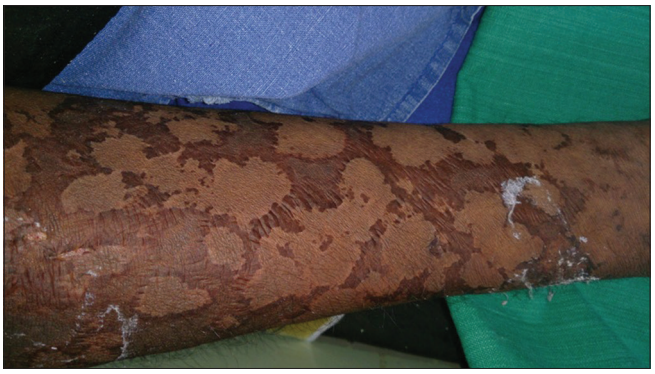


Figure 2: Livedo racemosa

lead to increased production of procoagulant substances such as tissue factor, plasminogen activator inhibitor 1, and endothelin. Increased tissue factor expression on endothelial cells induced by APL could be responsible, in part, for hypercoagulability and explains the thrombosis in both arterial and venous circulation that characterizes APS.

Amantadine has been reported to cause LR due to catecholamine-provoked arteriolar vasospasm.[5]

Livedoid vasculopathy is a rare ulcerative subtype of LRC due to fibrinolytic abnormalities and microcirculatory thrombosis.

LR preceded the onset of repeated attacks of pancreatitis in a patient with chronic pancreatitis.[8] Other conditions that are associated with LR include primary fibromyalgia and congenital hypogammaglobulinemia.[9,10]

LIVEDO RETICULARIS

LR may be differentiated into four distinct entities based on duration of the livedo pattern and its association with ambient temperature: Physiological, primary, idiopathic, and amantadine-induced LR.[3,11]

Physiologic LR, also known as cutis marmorata, mainly seen in young women, occurs commonly on the legs on exposure to cold temperature, with slow resolution on rewarming. An impairment of blood flow in cutaneous vessels causes the mottling of LR related to the vascular anatomy of normal skin.

Primary LR also has a fluctuant course, but differs from cutis marmorata in that changes in skin color are unrelated to ambient temperature.[11]

Idiopathic type is a persistent and unresolving form of LR.[11] The diagnosis is reached when no other pathological signs except LR are found. It rarely represents the early stage of APS or Sneddon's syndrome.

LIVEDO RACEMOSA

LRC is characterized by a striking violaceous net-like pattern of the skin similar to LR, but it differs by its location (more generalized and widespread, noninfiltrated, found on the limbs, trunk, and buttocks), its shape (irregular, broken, circular segments), and its biopsy results.[3,4,12] LRC is the classical sign of Sneddon's syndrome, but also seen in other disorders such as livedoid vasculopathy, APS, systemic lupus erythematosus (SLE) with or without APS essential thrombocythemia, thromboangiitis-obliterans, polycythemia vera, and polyarteritis nodosa. Ehrmann described that LRC was associated with a number of pathological conditions, compared with the physiological LR. The dermatology literature includes a number of pathologic conditions in the differential diagnosis of LR. Hence it is inferred that although the differential diagnosis of these two forms of livedo may be similar and overlapping, only APS has been associated with LRC.[13]

Cutis marmorata is the common cause of LR in infants followed by CMTC and transplacental transient vasculitis.[11]

The list of the abnormalities associated with CMTC are presented in Algorithm 1.[11]

Etiology of livedo reticularis/livedo racemosa

The list of the conditions associated with LR are presented in Algorithm 2.[11]

Hematologic/hypercoagulable antiphospholipid syndrome

The antiphospholipid syndrome is strictly defined as the presence of lupus anticoagulant antibodies or anticardiolipin antibodies and either vascular thrombosis or specific pregnancy complications.[14] There are numerous other antiphospholipid antibodies that may be associated with the clinical findings of the antiphospholipid syndrome, but are not included in the diagnostic criteria. The antiphospholipid syndrome is further subdivided into primary cases not associated with other diseases, and secondary cases associated with other diseases, most commonly systemic lupus erythematosus (SLE) other connective tissue diseases, drugs, and malignancy.[14]

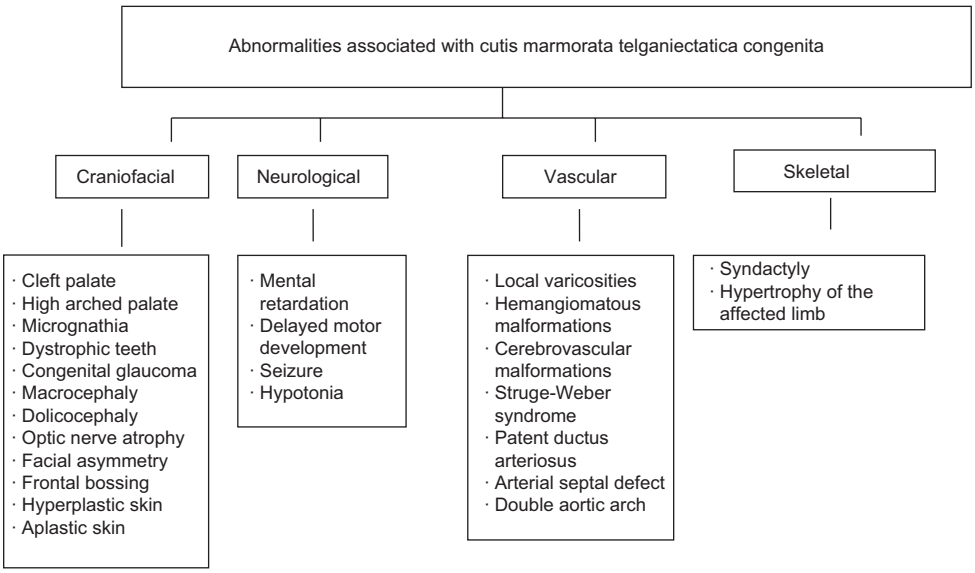
LR has been found to have a statistically significant association with the presence of antiphospholipid antibodies in the absence of SLE (i.e., primary antiphospholipid syndrome).[15] One study found that 40% of patients had LR as the first sign of the antiphospholipid syndrome. Given this, a patient presenting with LR should always be evaluated for antiphospholipid antibodies.[16] Similarly, consideration should be given to evaluating all patients with venous leg ulceration for antiphospholipid antibodies, because there is a demonstrated association between the two.[17]

More than 33% of patients with SLE may have antiphospholipid antibodies, but not all of these patients will have clinical symptoms of the antiphospholipid syndrome. LR is a significant preceding sign for development of neuropsychiatric lupus erythematosus.[18,19]

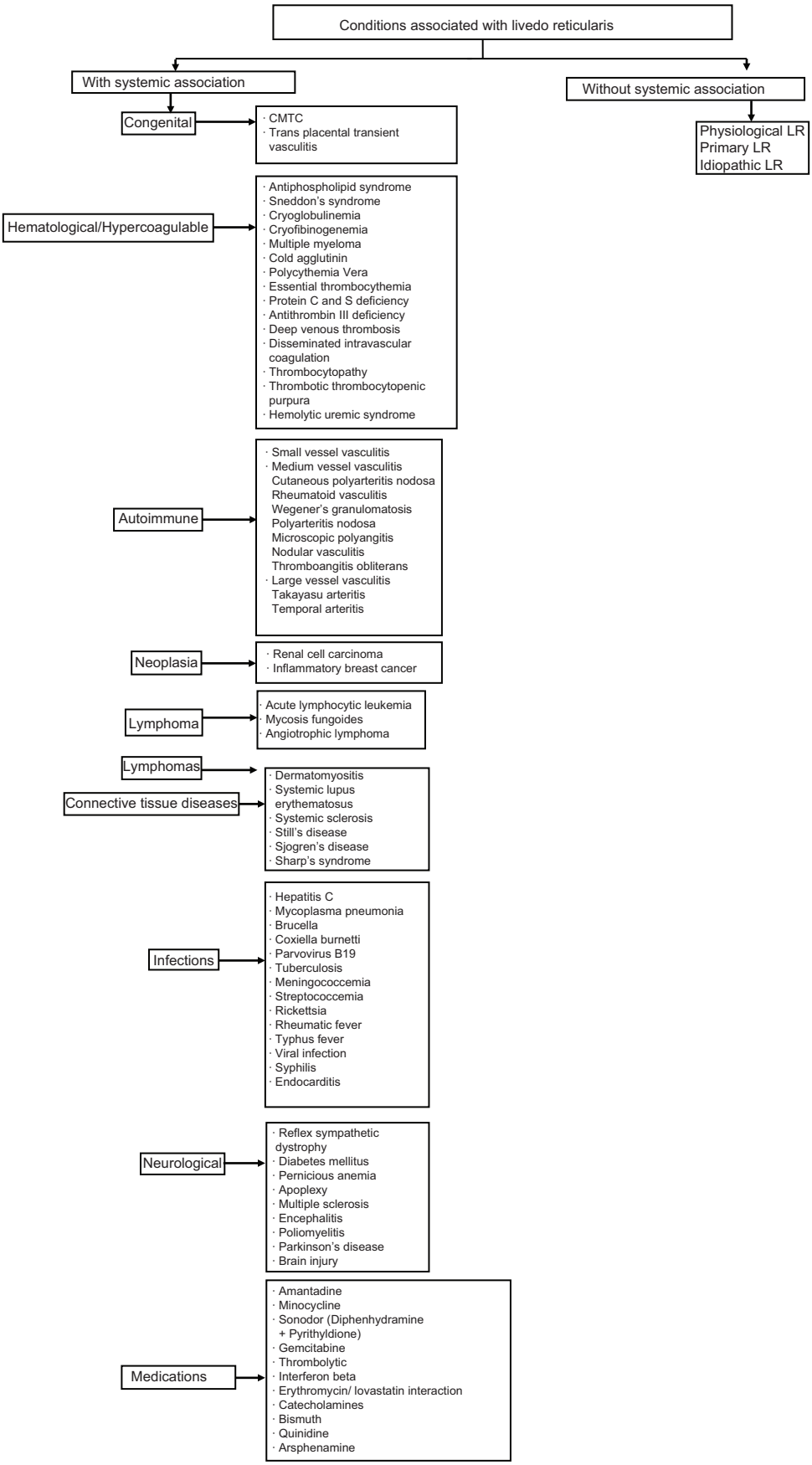
Patients with antiphospholipid syndrome associated with SLE were more likely to have arthritis, LR, thrombocytopenia, and leukopenia than those with primary antiphospholipid syndrome, whereas patients with primary antiphospholipid syndrome were more likely to have asymptomatic avascular necrosis of the femoral head.[20,21]

Endocrine and nutritional etiologies

Hormonal and dietary factors may produce LR. Hypothyroidism



Algorithm 1: Abnormalities associated with cutis marmorata telganiectatica congenital



Algorithm 2: Conditions associated with livedo reticularis

can be associated with LR that may resolve with appropriate replacement therapy.[22] Pseudohypoparathyroidism with associated hypercalcemia is reported to cause widespread calcification and, in turn, ischemic skin signs such as skin infarction and LR. The mechanism of livedo in hypoparathyroidism appears to be similar.[7] Cushing's disease is also reported to be associated with LR.[7] Pellagra is the only nutritional disorder associated with LR.[22]

Miscellaneous etiologies

Other disease states have been associated with LR, including cardiac failure and poliomyelitis.[7,23] Vascular stasis appears to be the best explanation for LR in these disorders.

Mechanical obstruction of blood flow can explain LR associated with widespread deposition of oxalate crystals.[24,25] The pathogenesis of LR associated with B-cell lymphoma,[26] cutaneous T-cell lymphoma,[1] and acute pancreatitis is unknown.[27]

Differential diagnosis

Erythema ab igne [Figure 3] is a heat-induced skin disorder that begins as a reversible LR, then, with continued heat exposure, evolves into a fixed reticulated hyperpigmentation in the same pattern. Other cutaneous eruptions may have a reticulated pattern, which might be confused with LR, including reticulated erythematous mucinosis and some viral exanthems, such as erythema infectiosum. Poikiloderma may present with a reticulate pattern (eg, mycosis fungoides, dermatomyositis, or GVHD); but, the presence of epidermal changes and telangiectasias will help distinguish these conditions from LR.[5]

Pathology

The histopathology of LR varies depending on the underlying cause. In idiopathic or physiologic forms, no histopathological changes are seen. In secondary causes of LR, a number of changes may occur, including vasculitis, calcium deposition within vessel walls (calciphylaxis), intravascular eosinophilic plugging (monoclonal cryoglobulinemia), intraluminal thrombosis (hypercoagulable states), cholesterol clefting (cholesterol emboli), and crystal deposition (oxalosis). In Sneddon's syndrome, vessel walls demonstrate endothelial inflammation and subendothelial myointimal hyperplasia with partial or complete occlusion of affected arterioles. To locate the histopathological changes, it is necessary to sample the affected arterioles. A large elliptical biopsy from the nondiscolored skin in the center of the net pattern is necessary, and serial sectioning may be required.[5]

SUMMARY

A variety of systemic diseases may be associated with LR. In adults, the most frequently associated diseases are characterized by vessel wall disease or intravascular obstruction. In the former group, lupus erythematosus is particularly important, because LR along with anticardiolipin antibodies are markers of serious cerebrovascular and renal disease. Appropriate evaluation of patients presenting with LR includes a careful history and physical examination. Laboratory investigations, including a complete blood count, platelets, coagulation profile, cryoproteins, antinuclear antibodies, and anticardiolipin antibodies, are useful screening methods for the important associated systemic diseases.

WORKUP

The evaluation of a patient presenting with LR can be a tough task. However, because there is potential for association with many different significant systemic diseases [Algorithm 2],[11] it is very important that every patient be evaluated carefully. Algorithms 3 and 4 help to evaluate an infant and adult presenting with LR/LRC.[11]

The first step is a detailed history and physical examination. The history of illness should specifically inquire about the location of LR, exacerbating and alleviating factors (eg, ambient temperature), duration of attacks, and cutaneous symptoms. Other areas of particular importance are questions regarding symptoms of autoimmune connective tissue disease, any personal or family history of thrombosis or hypercoagulability, new neurologic symptoms, and a general review of systems. Recent vascular procedures are important to be aware of, as are symptoms of recent infection. A general medical history inquiring about renal failure and medications, is also important. Risk factors for hepatitis C should also be elicited.

Particular areas of importance on physical examination include noting the location of LR and the presence of ulcerations or nodules as these two findings are suggestive of vasculitis.

Laboratory studies should be directed by the history and physical examination. With a few exceptions, extensive screening studies are extremely unlikely to be useful. One possible exception is a lupus anticoagulant panel, which is

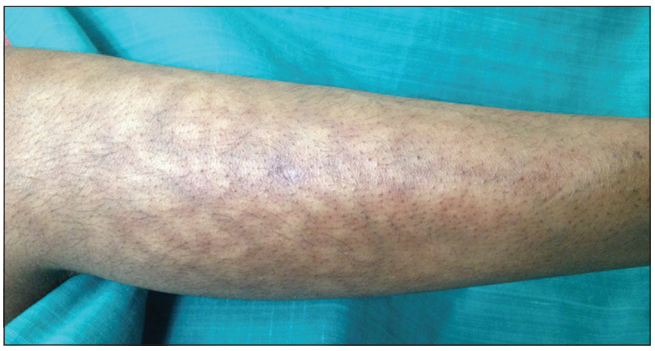
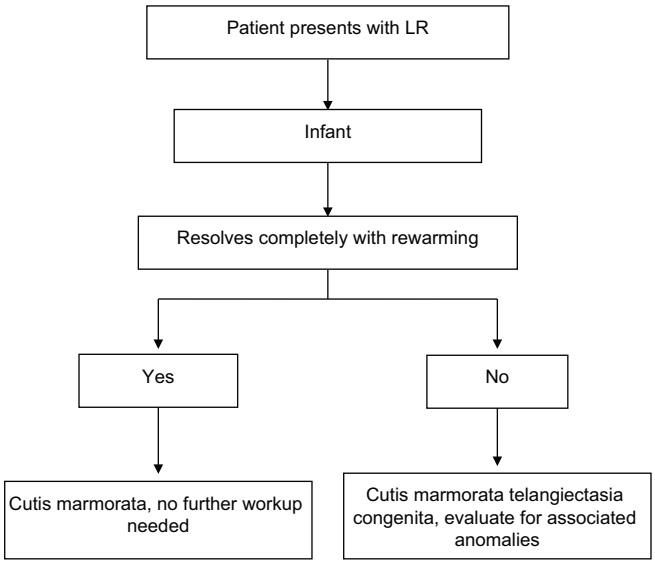


Figure 3: Erythema ab igne



Algorithm 3: Work up of infant presenting with LR

a reasonable study to consider in all patients presenting with LR that is not clearly and exclusively related to cold exposure.

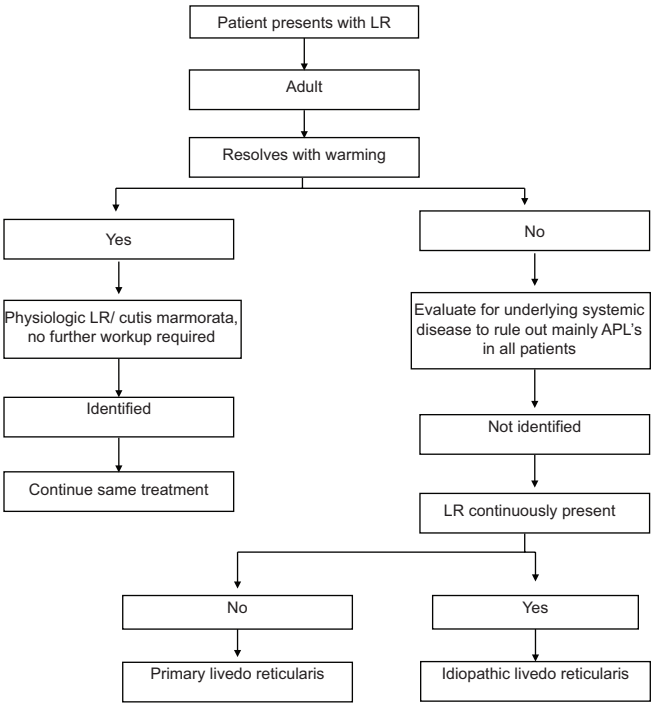
Skin biopsies have shown usefulness in diagnosing various causes of LR, specifically differentiating a vasculitis, vasculopathy, or normal tissue; however, these overall are of low yield. For this reason, when the cause of LR is unknown, and a systemic disorder is suggested, it is appropriate to perform several punch biopsies, at least one biopsy from a central blanched area and one from a peripheral bluish area. Multiple biopsies may increase diagnostic yield. If nodules and fixed purpuric areas are present, these areas should be biopsied.

It is important to understand that the goal of a biopsy is to obtain samples of the medium vessel found in the deep reticular dermis and subcutaneous fat. Therefore, either a wedge biopsy or a large punch biopsy is most likely to provide useful information.[11]

TREATMENT

Other than cold avoidance, medical treatment for primary LR is not needed. As a last resort, vasodilator therapy may be tried in the patient for cosmetic purpose. The symptoms may improve spontaneously with age.

Therapy for LRC should be directed toward the underlying disorder. Patients with LRC and the antiphospholipid antibody syndrome with thrombosis require anticoagulation therapy. Treatment of livedoid vasculopathy is not promising but potentially beneficial medications include anticoagulants, antiplatelet agents, immunosuppressants, pentoxifylline, danazol, and tissue plasminogen activator. Hyperbaric oxygen and psoralen and ultraviolet A light therapy have also been successfully utilized in some cases to treat livedoid vasculopathy.[5]



Algorithm 4: Work up of adult presenting with LR

CONCLUSION

LR presents a diagnostic challenge. We have reviewed the recent literature on this topic with suggestions for evaluation and classification of patients presenting with LR including algorithms. In cases of primary LR, no treatment is necessary. Patients diagnosed as idiopathic LR should avoid exposure to cold conditions. Conservative measures such as limb elevation and compression stocking may be helpful in symptomatic patients of LR. When underlying disorders are identified, management should be directed at treating these disorders.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

REFERENCES

1. Champion RH. Livedo reticularis: A review. Br J Dermatol 1965;77:167-79.
2. Ehrmann S. Ein gefassprozess bei lues. Wien Med Wochenschr 1907;57:777-82.
3. Kraemer M. Linden D, Berlit P. The spectrum of differential diagnosis in neurological patients with livedo reticularis and livedo racemosa. A literature review. J Neurol 2005;252:1155-66.
4. Lubach D, Schwabe C, Weissenborn K, Hartung K, Creutzig A, Drenk F. Livedo racemosa generalisata: An evaluation of thirty-four cases. J Am Acad Dermatol 1990;22:633-9.
5. Chadachan V, Dean SM, Eberhardt RT. Cutaneous changes in peripheral arterial vascular disease. In: Goldsmith LA, Katz SI, Gilchrest BA,

Paller AS, Wolff K, editors. Fitzpatrick's Dermatology in General Medicine. 8th ed. USA: McGraw-Hill; 2012.p. 2106-8.
6. Uthman IW, Khamashta MA. Livedo racemosa: A striking dermatological sign for the antiphospholipid syndrome. J Rheumatol 2006;33:2379-82.
7. Copeman PW. Livedo reticularis. Signs in the skin of disturbance of blood viscosity and of blood flow. Br J Dermatol 1975;93:519-29.
8. Gould JW, Hlems SE, Schulz SM, Stevens SR. Relapsing livedo reticularis in the setting of chronic pancreatitis. J Am Acad Dermatol 1998;39:1035-6.
9. Pay S, Calgüneri M, Calişkaner Z, Dinç A, Apraş S, Ertenli I, *et al*. Evaluation of vascular injury with proinflammatory cytokines, thrombomodulin and fibronectin in patients with primary fibromyalgia. Nagoya J Med Sci 2000;63:115-22.
10. Genovese A, Spadora G, Marone G. Livedo reticularis and congenital hypogammaglobulinemia. J Med 1992;23:78-80.
11. Gibbs MB, English JC 3rd, Zirwas MJ. Livedo reticularis: An update. J Am Acad Dermatol 2005;52;1009-19.
12. Francès C, Papo T, Wechsler B, Laporte Jl, Biousse V, Piette JC, Sneddon syndrome with or without antiphospholipid antibodies. A comparative study in 46 patients. Medicine (Baltimore) 1999;78:209-19.
13. Sepp N. Other vascular disorders. In: Bolognia J, Jorizzo J, Rapini R, editors. Dermatology. London, New York: Mosby; 2003. p. 1651-9.
14. Levine JS, Branch DW, Rauch J. The antiphospholipid syndrome. N Engl J Med 2002;346;752-63.
15. Naldi L, Locati F, Marchesi L, Cortelazzo S, Finazzi G, Galli M, *et al*. Cutaneous manifestations associated with antiphospholipid antibodies in patients with suspected primary antiphospholipid syndrome: A case-control study. Ann Rheum Dis 1993;52:219-22.
16. Kester S, McCarty DL, McCarty GA. The antiphospholipid antibody syndrome in the emergency department setting--livedo reticularis and recurrent venous thrombosis. Ann Emerg Med 1992;21:207-11.
17. Fink Am, Kottas-Heldenderg A, Mayer W, Partsch H, Bayer PM, Bednar R, *et al*. Lupus anticoagulant and venous leg ulceration. Br J Dermatol 2002;146:308-10.
18. Karassa FB, Loannidis JP, Touloumi G, Boki KA, Moutsopoulos HM. Risk factors for central nervous system involvement in systemic lupus erythematosus. QJM 2000;93:169-74.
19. West SG, Emlen W, Wener MH, Kotzin BL. Neuropsychiatric lupus erythematosus: A 10-year prospective study on the value of diagnostic tests. Am J Med 1995;99:153-63.
20. Cervera R, Piette JC, Font J, Khamashta MA, Shoenfeld Y, Camps MT, *et al*.; Euro-Phospholipid Project Group. Antiphospholipid syndrome: Clinical and immunologic manifestations and patterns of disease expression in a cohort of 1,000 patients. Arthritis Rheum 2002;46:1019-27.
21. Tektonidou MG, Malagari K, Vlachoyiannopoulos PG, Kelekis DA, Moutsopoulos HM. Asymptomatic avascular necrosis in patients with primary antiphospholipid syndrome in the absence of corticosteroid use: A prospective study by magnetic resonance imaging. Arthritis Rheum 2003;48:732-6.
22. Picasa DD, Pellegrini JR. Livedo reticularis. Cutis 1987;38:429-32.
23. Champion RH. Cutaneous reaction to cold. In: Rooks A, Wilkinson DS, Ebling FJ, editors. Textbook of Dermatology. 4th ed. Oxford: Blackwell; 1986. p. 627-31.
24. Baethge BA, Sanusi ID, Landreneau MD, Rohr MS, McDonald JC. Livedo reticularis and peripheral gangrene associated with primary hyperoxaluria. Arthritis Rheum 1988;31:1199-203.
25. Greer KE, Cooper PH, Campbell F, Westervelt FB Jr. Primary oxalosis with livedo reticularis. Arch Dermatol 1980;116:213-4.
26. Fishel B, Brenner S, Weiss S, Yaron M. POEMS syndrome associated with cryoglobulinemia, lymphoma, multiple seborrheic keratosis, and ichthyosis. J Am Acad Dermatol 1988;19:979-82.
27. Sigmund WJ, Shelley WB. Cutaneous manifestation of acute pancreatitis, with special reference to Livedo reticularis. N Engl J Med 1954;251:851-3.