Understanding Livedo Reticularis: A Unique Case of Cutis Marmorata Telangiectatica Congenita and Discussion of Differential Diagnoses and Work-Up

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Abstract

Livedo reticularis (LR) is a cutaneous vascular pattern that presents with reticular patch morphology. LR is a manifestation of a wide range of diseases, from idiopathic to systemic. We present a case with a rare distribution of congenital LR, or cutis marmorata telangiectatica congenita (CMTC). This is followed by a review of the extensive differential diagnoses to consider when LR is noted, in addition to work-up considerations and treatment options.

Introduction

Livedo reticularis (LR) describes a cutaneous vascular pattern that presents in a reticular or net-like configuration. The resulting mottled, reddish-blue to purple discoloration of skin is due to an accumulation of deoxygenated blood.[1] Decreased blood flow to the skin or decreased drainage from the skin results in an increase in deoxygenated blood trapped in the cutaneous venous plexus.[2] While this reaction is most commonly seen as a benign response to cold-induced vasospasm, known as cutis marmorata, LR can also be associated with congenital disease and systemic disorders that alter blood flow. Therefore, LR can serve as an indicator of underlying disease, and these diseases should be considered with persistent LR. We present a unique case of congenital LR, as well as a concise review of differential diagnoses, work-up, and treatment of the various causes of LR. The review aims to remind dermatologists to consider the many causes of this distinct pattern.

Case

A 69-year-old female with a past medical history of cutaneous squamous cell carcinoma, hypertension, anxiety, depression, and acid reflux presented to the dermatology clinic for a routine full body skin exam. On exam, red-purple patches and connecting rings in a lace-like pattern were noted on her bilateral upper (**Figure 1**) and lower extremities (**Figures 2, 3**). The findings were consistent with LR. The patient revealed that these lesions had been present since birth. She noted they worsen in cold temperatures and improve in warm temperatures but are always present and never completely resolve. The patient denied any associated symptoms including pain and tenderness. Family history revealed the patient's sister and mother have persistent LR as well. Review of systems was unremarkable. Current medications included lisinopril, pantoprazole, venlafaxine, and alprazolam. She denied history of autoimmune disease, significant malignancy, or infectious disease. The patient denied any prior work-up for LR. Given the history of LR since birth and significant family history, the patient was diagnosed with cutis marmorata telangiectatica congenita. The patient displayed the rarer presentation of generalized LR on bilateral upper and lower extremities without any associated anomalies. The patient denied any neurologic, ocular, or developmental disorders or symptoms and therefore did not elicit any additional work-up.

Discussion

Congenital Livedo Reticularis

Cutis marmorata telangiectatica congenita (CMTC)

CMTC presents with telangiectasias and atrophy of skin at birth or soon after.[3] A diagnosis of CMTC is made clinically because the histology is nonspecific, demonstrating dilated capillaries. Inheritance is sporadic; however, there are some familial reports.[4] CCCCCMTC is often localized to one extremity and is associated with soft-tissue atrophy and bone abnormalities underlying the affected area.[1,5] When localized to the abdomen, there is often a sharp demarcation line at midline. CMTC can also be generalized, in which case there is a higher risk of associated anomalies.[1] This form of LR may be associated with craniofacial, neurologic, cardiovascular, and ocular anomalies, such as cleft palate, congenital glaucoma, delayed motor development, mental retardation, Sturge-Weber syndrome, and hypertrophy of affected limb, in addition to many others.[1,6] Work-up should include regular-interval measurements of affected limb(s) and ophthalmology exams along with consistent monitoring of any additional abnormalities, such as neurologic symptoms. Improvement of CMTC often occurs as the child ages, and 20% of cases eventually completely resolve. Of those with complete resolution, 50% resolve by age 2.[3]

Primary Livedo Reticularis

Cutis marmorata

Also known as physiologic LR, cutis marmorata is the most common manifestation of LR and occurs as a response to cold.[1] This condition is most pronounced in neonates and infants and common in young children and fair-skinned females.[7] Cold exposure produces a physiologic arteriolar vasospasm

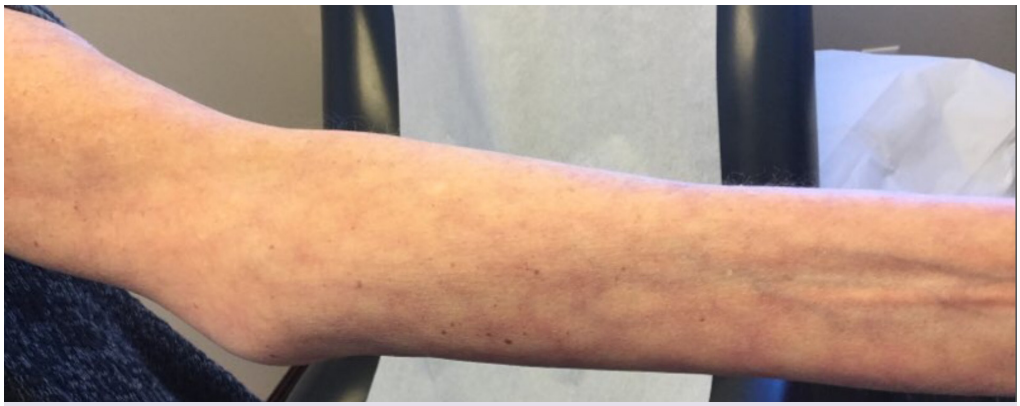
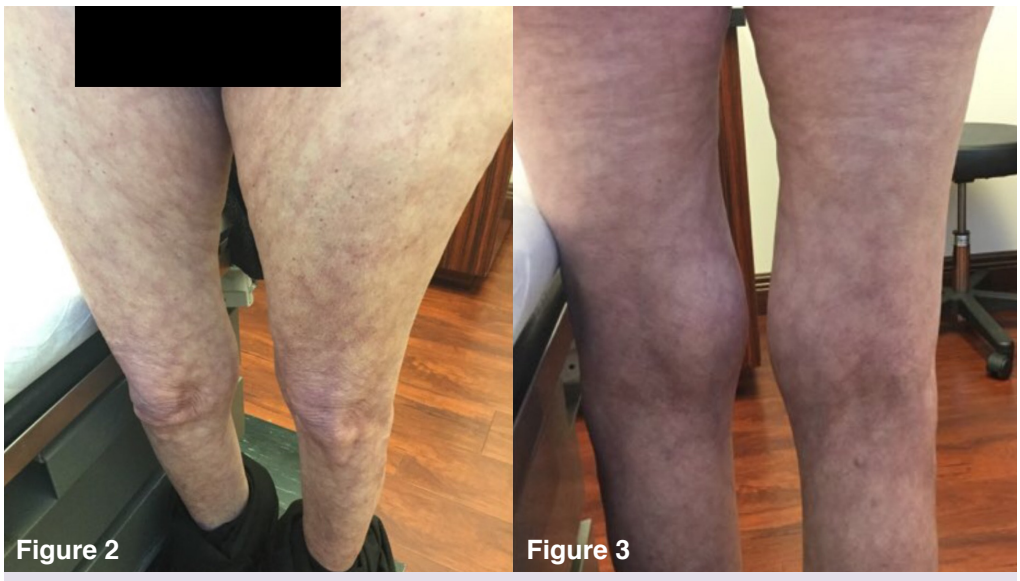


Figure 1. Livedo reticularis-like changes demonstrated on patient's upper extremity.



Figures 2, 3. Livedo reticularis-like changes demonstrated on patient's anterior and posterior lower extremities.

leading to the reversible skin changes seen in LR. Cutis marmorata has a predilection for extremities, particularly lower extremities. This condition resolves with re-warming. Avoiding cold exposure can prevent or lessen the appearance of cutis marmorata.[7]

Idiopathic Livedo Reticularis

When LR persists despite warming, idiopathic LR should be considered. This form of LR is the result of arterial vasospasm resulting in dermal hypoxia. While this condition is most commonly seen on lower extremities, involvement of the trunk and upper extremities can be seen. Limb elevation decreases the discoloration. This form of LR is temperature-independent and a benign finding.[7] It is not associated with underlying disease or pathology and is therefore a diagnosis of exclusion.[1] However, other forms of persistent LR associated with underlying disease should be ruled out before making this diagnosis.

Secondary Livedo Reticularis

Livedo reticularis vs. livedo racemosa

Livedo reticularis and livedo racemosa are often used interchangeably to describe a livedo pattern. However, these terms imply different clinical presentations, distribution, and underlying disease. While both indicate a net-like configuration, broken or irregular rings characterize livedo racemosa. In addition to their geometric differences, livedo racemosa is commonly seen on the trunk and buttocks, whereas LR is more common on the upper and lower extremities.[8] Livedo racemosa is always pathologic and commonly associated with Sneddon syndrome[9] and antiphospholipid syndrome.[10] Livedo racemosa can also be seen in other disorders, such as livedoid vasculopathy, systemic lupus erythematosus, essential thrombocythemia, thromboangiitis obliterans, polycythemia vera, and polyarteritis nodosa.[11]

Erythema Ab Igne

Erythema ab igne produces an LR-like pattern and is caused by extended heat exposure. It is often found on the thighs due to heat from laptops; lower back or abdomen due to heating pads; and feet due to overheating from the fireplace or furnace.[12] Erythema ab igne histologically resembles an actinic keratosis with keratinocyte atypia confined to the epidermis. Removing and avoiding exposure to the heat source is the most effective treatment. However, areas that do not resolve should be biopsied and evaluated for keratinocyte atypia and squamous cell carcinoma. If atypia is seen histologically, topical 5-fluorouracil cream should be considered for treatment.[13]

Vascular Causes of Livedo Reticularis

LR is associated with many vascular disorders. As stated prior, LR results from pooling of deoxygenated blood in the cutaneous venous plexus. Vasculitides and vasculopathies that result in decrease blood flow to or from the skin will consequentially increase the volume of deoxygenated blood in the venous plexus and result in LR.[1] Livedoid vasculopathy, formerly known as livedoid vasculitis, is thrombosis and ulceration of the lower extremities due to hyalinizing vascular disease. The etiology is not completely understood; however, no true vasculitis is evident on biopsy. End-stage livedoid vasculopathy results in atrophie blanche, a dermatologic finding of white stellate scars.[14]

A list of vasculitides associated with LR is summarized in **Table 1**.[1,5] Vasculitis should be considered when ulceration or nodules are present, particularly on the lower extremities.[1] Other vascular disorders or vasculopathies that result in LR are summarized in **Table 2**.[1,5] If vasculitis or vasculopathy is suspected, skin biopsies should be performed and preliminary labs initiated. Several cutaneous punch biopsies should be taken to increase diagnostic yield.[1] At least one biopsy should be taken from the central blanched area and one from a peripheral blue area. Biopsies from fixed or nodular areas are recommended.[1] Laboratory studies should reflect the history and physical. Appropriate labs may include complete blood count, BUN/Cr, liver function tests, urinary analysis, ASO titers, hepatitis profile, ESR, ANA, rheumatoid factor, c-ANCA, p-ANCA, complement levels (C3 and C4), cryoglobulins, and SPEP. If the biopsy is suggestive of vasculopathy, consider additional labs including cryofibrinogen, anticardiolipin antibodies, lupus anticoagulant, PT/PTT, DIC panel, RPR, fibrin and fibrinogen degradation products (FDP), D-dimer, fibrinogen, protein C and S deficiencies, and antithrombin 3.

Table 1. Vasculitides associated with livedo reticularis (LR)

Small Vessel	Medium Vessel	Large Vessel
Autoimmune	Polyarteritis nodosa	Takayasu's arteritis
	Rheumatoid vasculitis	Temporal arteritis
	Granulomatosis with polyangiitis	
	Microscopic polyangiitis	
	Nodular vasculitis	
	Thromboangiitis obliterans	

Table 2. Vasculopathies associated with LR

Hematologic/ Hypercoagulable	Embolic Diseases
Livedoid vasculopathy	Cholesterol emboli
Antiphospholipid syndrome	Septic emboli
Protein C and S deficiencies	Calciphylaxis
Antithrombin III deficiency	Atrial myxoma
Factor V Leiden mutation	Hyperoxaluria
Homocystinuria	
Sneddon syndrome	
Deep venous thrombosis	
Disseminated intravascular coagulation	
Thrombocythemia	
Polycythemia vera	
Cryoglobulinemia	
Cold agglutinins	
Cryofibrinogenemia	

Table 3. Malignancies associated with LR

Neoplasia	Lymphoma
Renal-cell carcinoma	Acute lymphocytic leukemia
Inflammatory breast cancer	Mycosis fungoides
	Angiotropic lymphoma
	Chronic lymphocytic lymphoma

Table 4.

Infectious etiologies associated with LR
Hepatitis C
Mycoplasma pneumonia
Brucella
Coxiella burnetii
Parvovirus B19
Tuberculosis
Meningococcemia
Streptococcemia
Rickettsia
Rheumatic fever
Typhus fever
Syphilis
Endocarditis

Malignant Causes of Livedo Reticularis

Neoplasms may result in LR due to various mechanisms characterized as vascular-occlusive. Malignancies associated with LR are listed in **Table 3**.[1,5] The cause of LR in angiotropic lymphomas, such as cutaneous B-cell and T-cell lymphomas, is not identified.[15]

Infectious Causes of Livedo Reticularis

Infectious etiologies of LR are listed in **Table 4**.[1] Mechanisms of vascular involvement are vast and not completely understood. Both *Mycoplasma* pneumonia and hepatitis C cause hyperviscosity that result in LR. *Mycoplasma* pneumonia can also cause cold hemagglutinins, whereas hepatitis C can result in mixed cryoglobulinemia. Both of these secondary states lead to LR as well.[16,17] Parvovirus B19 is thought to cause LR due to the vasodilatory effects of viral particles on vascular smooth-muscle cells.[18] Other evidence of infectious mechanisms for LR includes a case report of *Brucella spp*. that induced lower extremity LR. The authors suggest a possible hypersensitivity reaction as the cause.[19] Furthermore, the deposition of immune complexes eliciting LR was reported in a case of *Coxiella burnetii* infection.[20]

Neurologic Causes of Livedo Reticularis

Conditions that affect nerve conduction can lead to LR. For example, trauma to the peripheral nerves seen in reflex sympathetic dystrophy results in LR as well as sensory-motor dysfunction, pain, and dysautonomia.[21] Similarly, irritation of the brachial nerve plexus following insertion of a midline catheter into the basilic vein has been shown to cause LR in addition to edema, pain, and weakness.[22]

Medication-induced Livedo Reticularis

LR is seen as a reaction to certain systemic medications. This side effect is most commonly documented with amantadine. Amantadine-induced LR is highly variable, with incidence ranging from 2% to 90%, and is more common in women than men.[23] Amantadine-induced LR clears

with discontinuation of the drug; however, it is not necessary to discontinue the drug due to LR because it does not result in long-term sequela. Treatments to alleviate LR while continuing amantadine include limb elevation and compression stockings.[24] Other medications associated with drug-induced LR are listed in **Table 5**.[1] The appearance of LR subsides with discontinuation of drug.

Table 5.

Medications associated with LR
Amantadine
Minocycline
Diphenhydramine
Gemcitabine
Heparin
Thrombolytics
Interferon beta
Erythromycin/lovastatin interaction
Catecholamines
Bismuth
Quinidine
Arsphenamine

Conclusion

LR is a manifestation of a wide range of diseases, from idiopathic to systemic. LR most commonly is seen in cold-exposed areas, areas exposed to long-term heat, and as an idiopathic finding. Other causes of LR that should be considered are vasculitis, vasculopathies, medication side effect, infectious diseases, neoplastic etiologies, and neurologic diseases. Lastly, LR at birth is seen in congenital genodermatoses such as cutis marmorata telangiectatica congenita (CMTC) and implies that a neuro-oculo-developmental work-up is necessary. The patient presented here had findings consistent with CMTC in a rare bilateral distribution. No evidence of neuro-oculo-developmental anomalies was noted and therefore no additional work-up was performed. It is important for clinicians to be cognizant of the wide differential diagnoses of LR and rule out any underlying systemic disease or drug exposure in persistent LR.

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