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Case Presentation

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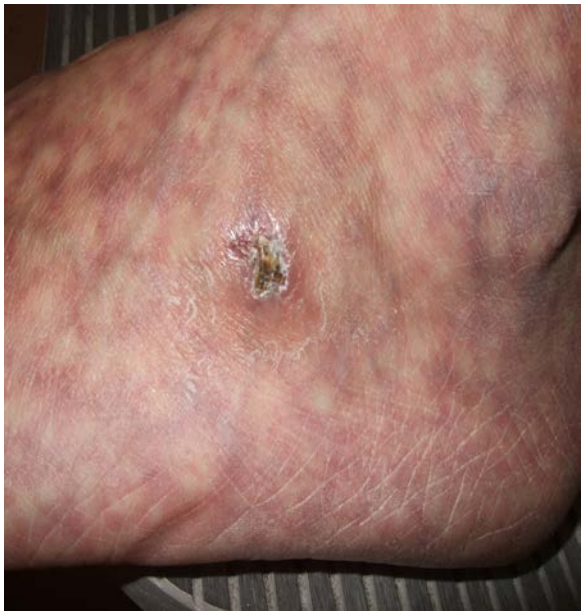
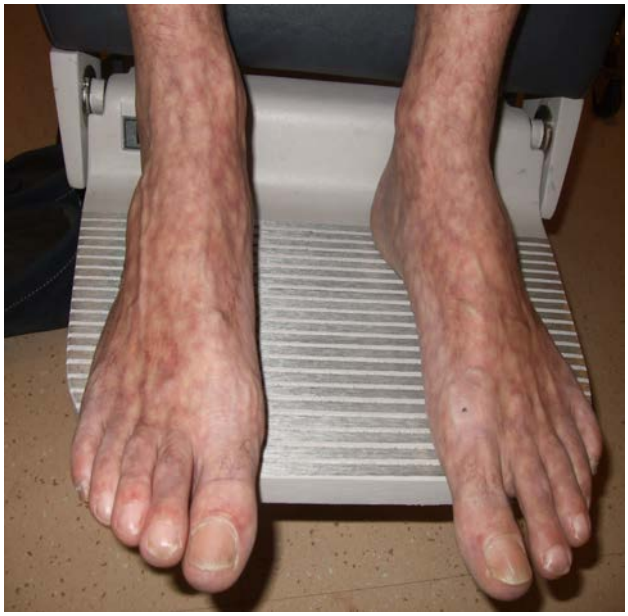
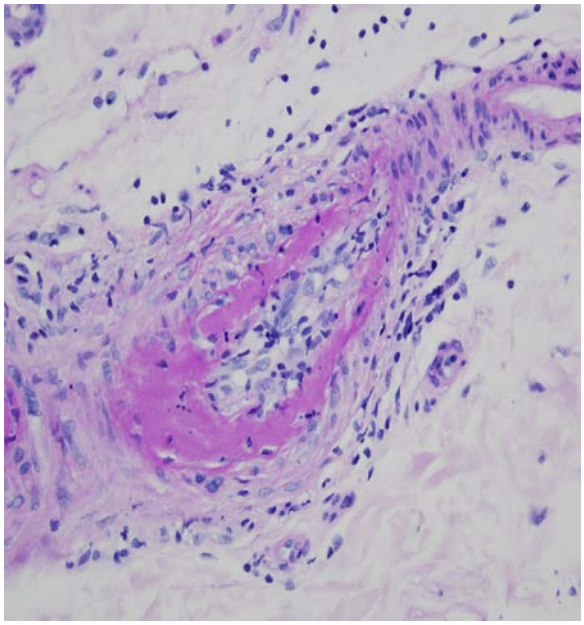
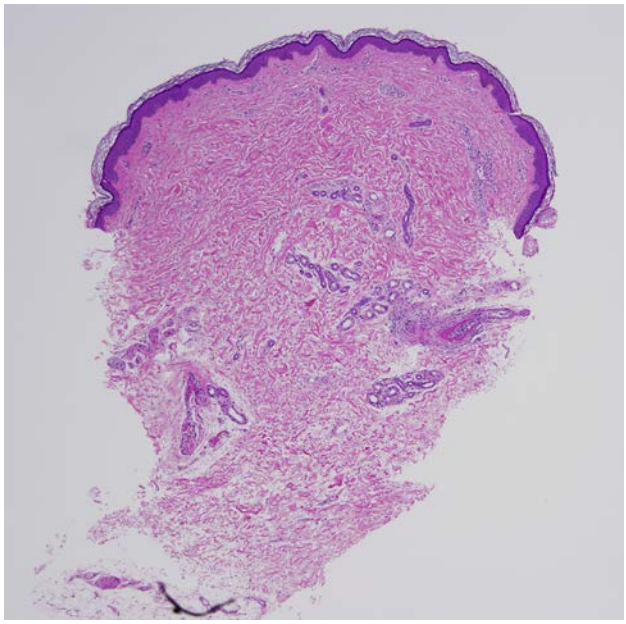
Abstract

Livedo reticularis (LR) is a net-like, violaceous, hyperpigmented pattern on the skin that reflects an underlying change in cutaneous blood flow. The causes of LR are many and most commonly include connective tissue diseases, vasculitis, hypercoagulability, and embolic events. We describe a 49-year-old man who presented with painful LR and ulcers on the lower extremities as a manifestation of chronic natural killer cell leukemia (CNKL). There have been only a few cases previously reported in the literature. We report an additional case of a patient with both LR and CNKL and suggest a possible mechanism that explains this association.









Case synopsis

A 49-year-old man presented to the New York University Dermatologic Associates for evaluation of a persistent discoloration on the legs and arms that had been present for 18 months and that was associated with severe pain. The discoloration started on the feet and then progressed to include the upper arms. In the three months prior to presentation he developed soreness on the lateral aspects of the feet that progressed to ulcers. He had been using topical lidocaine jelly without substantial relief. Two punch biopsies were obtained for hematoxylin and eosin staining and direct immunofluorescence studies.

Physical Examination: On the dorsal aspects of the feet there was a reticulated, net-like, pink-to-violaceous pattern of discoloration that extended to the ankles. A similar, although less pronounced, pattern was noticeable on the distal aspects of the forearms. On the lateral aspects of the feet were 1-cm, triangular-shaped, hyperkeratotic, hemorrhagic crusts at the site of healing superficial ulcers.

Laboratory Data: A complete white-cell count was normal with 59% lymphocytes and 25% neutrophils. Cardiolipin antibodies, cryoglobulins, hepatitis B antigen, and antineutrophil cytoplasmic antibodies were negative. Serum protein electrophoresis, immunofixation, lipid studies, and lactate dehydrogenase were normal. The antinuclear antibody titer was 1:40 with a speckled pattern. Flow cytometry of peripheral blood showed a large population of atypical natural killer (NK) T cells, with the following immunophenotype: CD2, CD7, CD57, CD158B positive; CD3, CD5, CD16, CD56, and CD158A/E negative. The T-cell population expressed pan-T-cell markers in a non-aberrant fashion with a normal CD4/CD8 ratio. Molecular studies showed a T-cell receptor gamma chain rearrangement and negative Epstein Barr Virus.

Histopathology: There is a sparse, superficial and mid-dermal perivascular infiltrate that is comprised predominantly of lymphocytes. A fibrin thrombus is noted that occludes the lumen of a blood vessel in the mid reticular dermis, which is highlighted by a periodic acid-Schiff with diastase stain.

Diagnosis: Livedo reticularis in the setting of chronic natural killer (NK) cell leukemia

Discussion: Livedo reticularis (LR) is a net-like, violaceous, hyperpigmented pattern on the skin that reflects an underlying change in cutaneous blood flow. Physiologic LR or cutis marmorata represents a normal vasospastic response in healthy individuals that occurs upon cold exposure. In contrast to pathologic LR, physiologic LR will disappear upon warming. Pathologic LR can be further divided into congenital and acquired causes. Congenital LR or cutis marmorata telangiectasia congenita (CMTC) is noted at birth, typically is limited to one extremity, and can be associated with limb asymmetry and neurologic abnormalities [1]. The causes of acquired LR include conditions that result in vasospasm, reduced intravascular flow, vessel-wall pathology, and vessel obstruction as well as medications, neoplasms, and some neurologic disorders. Livedo racemosa refers to a pattern of large, broken rings that occur typically on the trunk and proximal aspects of the extremities and that most commonly are associated with Sneddon syndrome [2].

The striking appearance of livedo reticularis results from the arrangement of the underlying cutaneous vasculature in which arterioles oriented perpendicular to the skin surface create a network of 1-to-3-cm cones of arterial predominance throughout the skin [1]. Interspersed between the circular bases of the arterial cones is a net-like, lacy pattern of venous predominance that becomes clinically apparent in conditions that reduce blood flow to or from the skin and that result in venous congestion. The underlying pathology in LR is not the net-like vascular pattern in the skin but rather the obstruction or inflammation in the arteriole; thus diagnostic biopsies are generally taken from the white, center of the ring and not from the actual rings themselves. There are some, however, who feel it is more appropriate to take multiple biopsies from the inner and outer portions of the ring [3]. It is often necessary to take a large elliptical biopsy (or several biopsies) from the center of the ring in order to capture the representative histopathologic findings that account for the LR.

The most common cause of LR is vasospasm that is associated with connective tissue disease and Raynaud phenomenon [1]. In patients with malignant conditions, LR is often the result of decreased intraluminal flow that is secondary to paraproteins or abnormal blood components as in the case of essential thrombocytopenia or polycythemia vera [4, 5]. In our patient with NK cell leukemia, the presence of a normal total white-cell count and a normal serum protein electrophoresis suggests that a mechanism other than decreased intraluminal flow may be responsible for the painful livedo. LR can also be caused by vessel wall pathology that alters cutaneous blood flow as is the case in the medium-sized arteriole vasculitis of cutaneous polyarteritis nodosa or cryoglobulinemic vasculitis. The presence of ulcers or nodules is particularly suggestive of vasculitis [3].

There is one prior case report in the literature of a patient with NK cell leukemia who presented with generalized livedo reticularis and histopathologic findings that were consistent with polyarteritis nodosa [6]. The authors hypothesized that the specific expression pattern of killer cell immunoglobulin-like receptors (KIRs) that were demonstrated on flow cytometry, specifically the

loss of inhibitory CD158a, CD158b, and CD158e, may lead to unopposed NK-cell activation and resulting vascular inflammation. Our patient's NK cell population also was negative for CD158a and CD158e, which suggests that the livedo reticularis also may have been a result of NK-cell-induced vascular inflammation. However, there was only a sparse, perivascular infiltrate noted on histopathologic examination without evidence of leukocytoclasia, which is less consistent with vasculitis and more consistent with a thrombo-occlusive process, such as atrophie blanche. NK cells have innate functions of cytotoxicity and cytokine release, but data suggest that they also may play a role in the autoimmune response [7]. Thus, it is possible that the specific aberrant NK cell immunophenotype present in our patient results in the release of cytokines that promote enhanced fibrin formation or platelet dysfunction. Another possibility is that an autoimmune response, which is mediated by the KIRs, promotes a pro-coagulant state.

The evaluation for a patient with pathologic LR is focused on determining the underlying etiology, which most commonly includes connective tissue disease, hypercoagulable states, vasculitis, and intraluminal obstruction. Laboratory studies should be guided by the history and physical examination, with a complete blood count, comprehensive metabolic panel, coagulation studies, proteins C and S, lupus anticoagulant, antiphospholipid antibodies, cryoglobulins, antinuclear antibodies, rheumatoid factor, cytoplasmic and perinuclear antineutrophilic autoantibodies, and serum immunoprotein electrophoresis [8]. Skin biopsies may be useful in categorizing the underlying etiology of the LR as vasculitic or vasculopathic. However, the diagnostic yield often is low [3]. Histopathologic findings of LR depend on the underlying etiology and include vessel wall thickening, thrombi, arteriolar obliteration, and red blood cell (RBC) sludging [9]. In a study of 16 patients with LR who had biopsies performed from both the white center of the ring and the violaceous border of the ring, there were no appreciable differences in thrombi, arterial obliteration, or RBC aggregates between the blanched center and the violaceous ring [9]. Thus, the authors concluded that multiple, deep punch biopsies should be obtained from both areas to increase the chances of identifying the pertinent histopathologic features.

The treatment of LR is directed at the underlying disorder. Conservative intervention, such as limb elevation or compression stockings, may provide symptomatic relief in some patients [3]. Unfortunately, treatment of the causative disorder may not always provide relief; such is the case in our patient who continues to suffer from disabling, painful livedo reticularis in spite of several interventions for his NK cell leukemia. Livedo reticularis is an important cutaneous finding to recognize because early intervention and treatment of underlying disorders may prevent potentially fatal thrombotic or hemorrhagic events.

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