Clinical Manifestations and Management of Livedoid Vasculopathy

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Abstract
Livedoid vasculopathy (LV) is an extremely rare and distinct hyalinizing vascular disease affecting only one in 100,000 individuals per year.1,2 Formerly described by Feldaker in 1955 as livedo reticularis with summer ulcerations, LV is a unique non-inflammatory condition that manifests with thrombi formation and painful ulceration of the lower extremities.3 Clinically, the disease often displays a triad of livedo racemosa, slow-healing ulcerations, and atrophie blanche scarring.4 Although still not fully understood, the primary pathogenic mechanism is related to intraluminal thrombosis of the dermal microvessels causing occlusion and tissue hypoxia.4 We review a case in which the patient had LV undiagnosed and therefore inappropriately treated for more than 20 years. To reduce the current average five-year period from presentation to diagnosis, and to improve management options, we review the typical presentation, pathogenesis, histology, and treatment of LV.4

Case Report
A 62-year-old Caucasian male presented in an assisted living facility setting with chronic, right-lower-extremity ulcers present for more than 20 years. The patient had a past medical history of chronic osteomyelitis, hypertension, and a below-the-knee amputation of the left lower extremity secondary to a motorcycle accident. He denied having seen a primary care physician for more than 15 years as well as any medications, vitamins or supplements. Social history was significant for “many years” of tobacco use, heavy alcohol use, inconsistent housing with reoccurring assisted-living-facility admissions, low economic status, and medical non-adherence. The patient reported that throughout the last 20 years his wound-care management for these lesions was limited to the periods of time in which he was living in assisted-living facilities.

Upon physical exam, the patient was found to have a wound on the right medial malleolus measuring 6.4 cm x 4.0 cm x 0.7 cm with moderate serous exudate, approximately 30% yellow necrosis and 70% granulation, with macerated wound margins (Figure 1), and a second wound on the right lateral malleolus measuring 6.0 cm x 5.5 cm x 0.4 cm with moderate serous exudate, approximately 20% sloughing tissue and 80% granulation (Figure 2). The patient was treated for one year, although inconsistently due to housing circumstances, with a series of necrotic-tissue debridements and a variety of topical antibiotics; however, despite therapy, the wounds failed to close. Throughout the duration of management, the patient repeatedly refused biopsy and hyperbaric oxygen therapy. Following one year of multiple topical antibiotics and debridement treatment resulting in minimal improvement, the patient finally consented to biopsy. The pathology report identified ulceration with fibrin in vessel walls associated with stasis dermatitis characterized by thick-walled capillaries and hemosiderin deposition consistent with livedoid vasculopathy (Figures 3). The patient refused any further treatment and was lost to follow-up.

Discussion
Livedoid vasculopathy affects women three times more than men, with a median age of 45 years, though it can vary from ages 10 to 85.1,2 Likely secondary to the rarity of the condition, there is much discussion regarding the name of the condition, as authors have written about LV under a wide array of monikers. Common names used synonymously with livedoid vasculopathy include: livedoid vasculitis, segmental hyalinizing vasculitis, livedo reticularis with summer ulcerations, and atrophie blanche en plaque.1,4 Although commonly used, the denotation of “vasculitis” is a bit misleading, since the primary mechanism of action is not actually inflammation.4 Due to the bilateral and symmetrical lower-extremity distribution of the eruptions, LV has also been nicknamed “PURPLE syndrome” (Painful Purpuric Ulcers with Reticular Pattern of the Lower Extremities).4 The pathogenesis of LV is not yet fully understood, but there is a consensus that it consists of dermal blood-vessel thrombosis leading to superficial tissue ischemia and necrosis, thus propagating pain and ulceration.1 According to the Virchow triad theory, the three factors that contribute to the development of thrombosis, and therefore theoretically LV, include endothelial damage, inadequate blood flow, and hypercoagulability.2,5 It has been demonstrated that patients with LV exhibit decreased flow-mediated vasodilation of the brachial artery, signifying endothelial dysfunction.5 A decreased production or activity of nitrous oxide in endothelial cells has been detected in some cases, supporting the contribution of endothelial damage to LV.6 Additionally, the fact that fibrinolitics, antiplatelets and thrombolytic

Figure 1. Right medial malleolus. 6.4 cm x 4.0 cm x 0.7 cm ulceration exhibiting moderate serous exudate, approximately 30% yellow necrosis, 70% granulation, and macerated wound margins.

Figure 2. Right lateral malleolus. 6.0 cm x 5.5 cm x 0.4 cm ulcerations with moderate serous exudate, approximately 20% sloughing tissue and 80% granulation.
agents have shown to have a positive effect on LV patients demonstrates the contribution of hypercoagulability and decreased blood flow to its pathogenesis. In fact, several conditions may lead to the creation of these three contributing factors. Patients with LV may be categorized as having primary (idiopathic) LV or secondary LV, in which a known underlying condition is the root of the disease. A thorough investigation must be performed in any patient suspected to have LV to rule out conditions such as systemic lupus erythematosus, scleroderma, protein C or S deficiency, factor V Leiden, homocysteinemia, sickle-cell anemia, cryoglobulinemia, cryofibrinogenemia, increased antithrombin, underlying malignancy, altered fibrinolysis, or platelet activation that may be the underlying cause of the hypercoagulability or occlusion. However, unknown individual factors must exist for the development of LV given that, for instance, few people with protein C deficiency develop LV.

Patients with LV clinically present with bilateral, painful, “punched out” ulcerations that are slow to heal and result in stellate atrophic scar tissue. Affected regions may also demonstrate erythema, telangiectasia, hyperpigmentation, and possibly purpura. The triad of livedo racemosa, ulcerations, and atrophic blanche characterizes the unique clinical presentation of LV. Livedo racemosa, a fixed, irregular, reticular pattern on skin, is secondary to the microcirculation disorder and results in local tissue hypoxia and possible necrosis. Although LV is not the only disorder in which livedo racemosa may be seen, it is commonly clinically regarded as an indicator of impending LV. The cutaneous ischemia leads to painful purpuric and erythematous plaques and papules frequently evolving into punched-out ulcerations. The painful eruptions are typically located bilaterally and symmetrically on the lower extremities, most frequently on the malleoli. As the ulcers begin to heal, at approximately four months, they result in stellate, white, atrophic scars around their borders, known as atrophie blanche, resulting in permanent fibrosclerosis of the skin. Additionally, patients may complain of parenthesis or hyperesthesia, indicating potential mononeuritis multiplex, likely secondary to the deposition of fibrin and thrombin in the vasa nervorum resulting in ischemia.

Lower-extremity, reticulated, ulcerated lesions that closely resemble LV and should be considered in the differential diagnosis include: lupus-associated antiphospholipid syndrome, sickle-cell anemia leg ulcers, venous stasis with varicosities, hydroxyurea-related ulcerations, dysproteinemia, vasculitis, microscopic polyarteritis, polyarteritis nodosa, granulomatous vasculitis, and peripheral vascular disease.

The cardinal histologic findings of LV are seen at the dermal-epidermal junction and consist of: deposition of fibrinoid material in the vascular lumen, hyalinization of the vessel wall, tissue infarctions and lack of vasculitis. More specifically, the fibrinoid thrombus is found in the lumen of small vessels of the superficial dermis. This may be accompanied by ulceration or infarction of the overlying epidermis. The fibrinoid material may similarly be found on the vessel walls and in the surrounding stroma, creating fibrinoid rings. Hyalinized walls and endothelial proliferation may also be identified, in addition to extravasated erythrocytes in the stroma that may indicate microhemorrhage. Direct immunofluorescence may show immunoglobulin, fibrin and complement deposition in the superficial vessels; however, these are not specific to LV and must be supported by other findings. Livedoid vasculopathy is diagnosed based on a combination of clinical and histopathological findings. The first step in the clinical workup should be to rule out venous insufficiency and other common causes of atrophie blanche. A detailed personal and family history of hypercoagulable disorders, fibrinolytic disorders, connective-tissue disorders and inflammatory disease should be performed. Chronic venous insufficiency may be evaluated by the presence of varicose veins, ochre dermatitis, lower-extremity edema and an abnormal venous Doppler ultrasound. Peripheral artery disease may also be associated with LV and may present with claudication, painful ulcers, pale and cold extremities and abnormal arterial Doppler ultrasound. Specific laboratory analysis is dependent on clinical presentation and is targeted towards the exclusion of the conditions that are associated with LV. If a connective-tissue disease is suspected based on family and/or personal history and presentation, consider laboratory analyses for antinuclear antibodies, antiphospholipid antibodies, anti-beta-2 glycoprotein I, anticardiolipin antibodies, LMW heparin induced inhibitor, antiphosphatidylserine. Laboratory analyses for hypercoagulable or fibrinolytic disorders may include factor V Leiden, prothrombin G20210A mutation, elevated factor VIII level, protein C and S deficiency, antithrombin III deficiency, hyperhomocysteinemia, plasminogen-activator inhibitor or reduction in plasminogen-activator activity, monoclonal cryoglobulinemia, and cryofibrinogenemia. For paraproteinemias, laboratory workup may include determination of immunoglobulin, kappa and lambda chain levels, protein electrophoresis and immunofixation. Additionally, polyclonal cryoglobulins may be associated with hepatitis B and C and should also be taken into consideration.

Biopsy of tissue for regular histology and immunofluorescence is required for diagnosis. Deposition of fibrin, immunoglobulin (IgG, IgM) and complement C3 may be detected by immunofluorescence. Biopsies revealing intraluminal thrombosis, endothelial proliferation, and hyalinized degeneration of the dermal vessels provide a definitive diagnosis of LV. However, due to the focal and segmental nature of LV, this “classic” presentation may not be visualized with a single biopsy. It is important to note that biopsies actually complicate the healing of the ulcerations. Therefore, it is debatable whether practitioners should opt to obtain repeated biopsies in order to obtain all three histological patterns. Special attention should be given to the biopsy method in which specimens are obtained. Small, wedge-shaped tissue samples obtained from the periphery of the ulcer and including healthy adjacent tissue are often preferred. This is due to the fact that the base of the ulcer predominantly demonstrates inflammation from tissue repair and granulation.
There is currently no agreed-upon treatment protocol for the diagnosis of LV, and current therapeutic regimens remain largely understudied, compounding the fact that in many cases, LV is difficult to treat. Management should be focused on preventing further propagation of microthrombi, the pathological cause of the disease, and addressing any underlying coagulation disorders. Although mostly anecdotal, long-term antiplatelet therapy with acetylsalicylic acid, dipyridamole, cilostazol, thienopyridines, or prostacyclin analogues have been found to be relatively equivalent in improving coagulation in order to improve cutaneous oxygenation. There is still no agreed-upon dose for anti-coagulation in the treatment of LV, though most studies and reports that have achieved wound resolution administered dosages indicated for deep-vein thrombosis prevention.

A review of the literature yielded a wide assortment of other approaches that have been employed with varying results. Anabolic agents, such as danazol and stanozolol, have been demonstrated as beneficial in many reported cases. In patients with systemic lupus erythematosus, antimalarials should be employed. Systemic phototherapy with PUVA, consisting of oral 8-methoxypsorale and UVA therapy, as well as cyclosporine and intravenous immunoglobulin are being explored as possible therapies. Incorporation of antibiotics, specifically doxycycline, has been reviewed for its potential therapeutic effects in LV along with its ability to safeguard against infection. Doxycycline, a second-generation tetracycline, is known to provide anti-inflammatory and anti-microbial protection; however, its use has been reported to show improvement in patients with LV who have failed other treatment. The mechanism for which doxycycline may be beneficial in a thrombotic condition is unknown, and the use of doxycycline is not meant to replace anti-thrombotic agents in patients with known hypercoagulability. Also, as a treatment adjunct, hyperbaric oxygen therapy shows promising results, facilitating the body’s innate healing response and relieving pain. Proper wound care, such as with zinc oxide, glycercin, gelatin dressings, frequent dressing changes, and debridement of necrotic tissue is paramount. Pressure on the ulcer should be relieved with leg elevation utilizing products such as foam wedges, pillows or rotation devices if necessary. Due to the association of LV with venous disease, compression stockings are an important addition to therapy as they have been shown to stimulate fibrinolytic activity. However, in patients at high risk for peripheral arterial disease, ankle brachial pressure index must first be completed before safely proceeding with compression.

Dredriment may be achieved through mechanical, autolytic, or enzymatic mechanisms. Ideal wound care strategy is to cleanse with normal saline, in the least traumatic manner possible, and then apply occlusive dressings that provide a moist environment. Silicone adhesives along with room-temperature wet compresses will minimize the trauma associated with dressing changes. Patients should be frequently monitored for signs of infection, including leukocytosis, fever, or inflammation, until wound resolution is achieved. Additionally, smoking-cessation education, proper diet, and management of systemic conditions are essential in order to facilitate proper wound healing.

As discussed, LV is characterized clinically by intensely painful, recurring ulcerations. However, pain management in LV has not been thoroughly studied and is, at most, modestly examined in the literature. Pain should be appropriately assessed, and conservative methods, such as gentle handling with appropriately absorbent dressings, ought to be employed first to minimize pain exposure. However, pain management may be necessary as part of the treatment protocol for individuals with severe discomfort. Prior reports have found three to six weeks of aspirin (up to 325 mg per day) along with dipyridamole to be an effective treatment combination, providing pain relief while inhibiting thrombus. It is important to note that aspirin should be avoided in patients being managed with warfarin. However, it is important to identify the root of the patient’s pain. Pain secondary to the ulcer is typically limited to the margins and intensified during dressing changes and debridement. Pain resulting from vascular occlusion is more complicated, as it is both nociceptive and neuropathic in nature. In these cases, pain control strategies should be obtained using the World Health Organization analgesic ladder.

Conclusion

Livedoid vasculopathy is a painful, chronic, and recurrent condition that may leave the patient severely debilitated if not recognized early and treated properly. With a current five-year average between onset of symptoms and diagnosis, patients are typically left to suffer through painful ulcers with permanent atrophic blanche. Although a rare condition, it is for these reasons that it is critical for clinicians to have LV in their differential diagnoses of lower-extremity purura with reticulated stellate ulcerations that are difficult or slow to heal. Once identified, treatment modalities are aimed at improving microcirculation, preventing infection, wound care, and pain control.

Acknowledgements

The authors would like to thank Jose Perez, DO, for the diagnosis of LV and his therapeutic efforts in the management of the discussed patient.

References


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