Livedoid vasculopathy: an intringuing cutaneous disease *

Vasculopatia livedoide: uma doença cutânea intrigante

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Abstract: Livedoid vasculopathy is a skin disease that occludes the blood vessels of the dermis. It has a pauciinflammatory or non-inflammatory nature. It is characterized by the presence of macular or papular, erythematous-purpuric lesions affecting the legs, especially the ankles and feet, and producing intensely painful ulcerations, which cause white atrophic scars called "atrophie blanche". This review includes studies and case reports found in the medical literature regarding the etiopathogenic associations of the disease, particularly those related to thrombophilia, their histopathological findings and the therapeutic approaches used in the difficult clinical management of these cases.
Keywords: Leg ulcer; Livedo reticularis; Thrombophilia; Thrombosis; Venous thrombosis

Resumo: A vasculopatia livedoide é uma afecção cutânea oclusiva dos vasos sanguíneos da derme, de caráter pauci-inflamatório ou não-inflamatório. Caracteriza-se pela presença de lesões maculosas ou papulosas, eritêmato-purpúricas, nas pernas, especialmente nos tornozelos e pés, as quais produzem ulcerações intensamente dolorosas, que originam cicatrizes atróficas esbranquiçadas, denominadas "atrofia branca". Nesta revisão, abordamos os estudos e relatos de caso da literatura médica referentes às associações etiopatogênicas da doença, particularmente as que se referem aos estados de trombofilia, seus achados histopatológicos e abordagens terapêuticas empregadas na difícil condução clínica destes casos.
Palavras-chave: Livedo reticular; Trombofilia; Trombose; Trombose venosa; Úlcera da perna

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INTRODUCTION

Livedoid vasculopathy (LV) is a dermatosis whose management can be challenging. This condition has extensive synonymy: livedo vasculitis, segmental hyalinizing vasculitis, livedoid vasculitis, livedo reticularis with summer ulcerations, livedo reticularis with winter ulcerations, Milian's white atrophy (*atrophie blanche*) and PURPLE (*painful purpuric ulcers with reticular pattern of the lower extremities*). [1-4]

From a clinical point of view, it is characterized by lesions that begin as painful punctate or lenticular purpuric macules and/or papules on the lower limbs, especially on the ankles and dorsum of the feet. These lesions usually undergo ulceration. Then, they heal slowly, over weeks or months, resulting in porcelain-white atrophic scars (white atrophy), punctate telangiectasia, and livedoid brownish pigmentation, usually accompanied by livedo racemosa. [1] The disease usually affects the legs bilaterally, often causing swelling in the lower third of the limbs. [5] The estimated prevalence of LV in the U.S. general population is around 1 case per 100,000 people per year. It especially affects the age group between 15 and 50 years old (mean 32 years) and females at a proportion of 2.4 to 3 women for every man. [6-9]

LV was originally described as a clinical manifestation of vasculitis. However, at present, the main physiopathogenic mechanism considered is a vaso-occlusive phenomenon due to intraluminal thrombosis of dermal venules[1]. Papi et al. substantiated this concept based on the clinical evolution of the disease, its improvement under antiplatelet and fibrinolytic therapy and on the detection of high levels of fibrinopeptide A. [1]

CLINICAL PRESENTATION

LV shows a chronic course with periodic and recurrent exacerbations. A physical examination may reveal lesions in different stages of evolution, usually associated with livedo racemosa. [8] During its evolution, purpuric and erythematous papular plaques and papules are formed. These plaques and papules are painful on palpation and sometimes initially itchy. Some lesions evolve to hemorrhagic vesicles. [5] Then, there is ulceration, which sometimes occurs as multiple ulcers individually measuring about 4 to 6 mm in diameter. They may also coalesce into large ulcers in a geographical form, which heal slowly, over about 3 to 4 months, with ivory-white stellate borders and atrophic center, presenting the morphological appearance of White Atrophy (Figures 1 and 2). [5,8] Peripheral punctate telangiectasias and slough appear in some areas that are about to ulcerate. [5] The lesions usually occur symmetrically on the legs and feet.

During its evolution, somewhat retractile, inflexible scars appear, causing true fibroesclerosis and determining stiffness of the affected skin. [5] These scars (atrophie blanche) are not pathognomonic of LV, as they may occur with other conditions such as venous stasis or some autoimmune connective tissue diseases (lupus erythematosus, dermatomyositis). [5]

Livedo racemosa (defined by the presence of an irregular reticular pattern of the skin) is often, but not always, associated with LV. It usually affects the lower limbs, but may affect the upper limbs in some patients (Figure 3). Pain is a constant characteristic in patients who experience episodes that culminate in ulceration, hampering their daily activities and causing intense suffering due to its ischemic character. Some patients experience symptoms of paresthesia or hyperesthesia, characterized as mononeuritis multiplex. [10] The involvement of the peripheral nervous system possibly occurs due to areas of multifocal ischemia, resulting from the deposition of fibrin and thrombin in the *vasa nervorum.* [10]

The presence of varicose veins in patients with LV ranges from 20 to 75%, and purpura pigmentosa chronica may occur in about 20% of the patients, especially early in the development of the disease. [5]

Etiopathogenesis

LV is the cutaneous manifestation of several diseases that lead to non-inflammatory thrombosis of dermal vessels. [9] Although there is no consensus, most authors who study this disease currently consider this

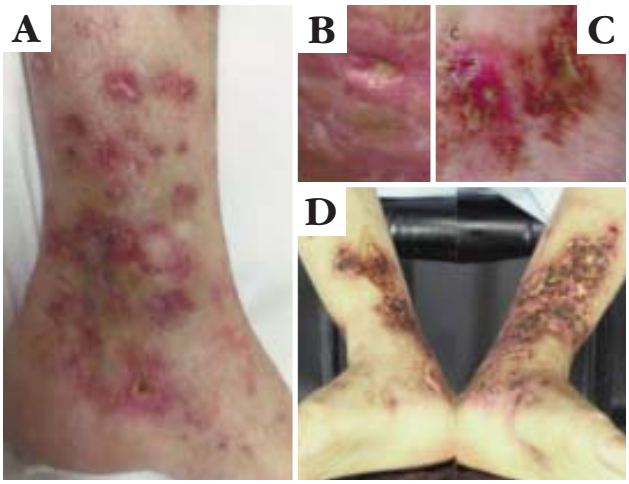

Figure 1: Livedoid Vasculopathy - lesions spread on the legs, especially on the ankles and feet. Punctate or lenticular ulcerations (A, B, C and D) coexist with larger ulcerations due to confluence of the former, surrounded by an erythematous and purpuric halo, sometimes covered with melicerous crusts (A, B and C) and sometimes with hematic crusts and necrotic slough (eschar) (D). Observe lesions in different stages of evolution

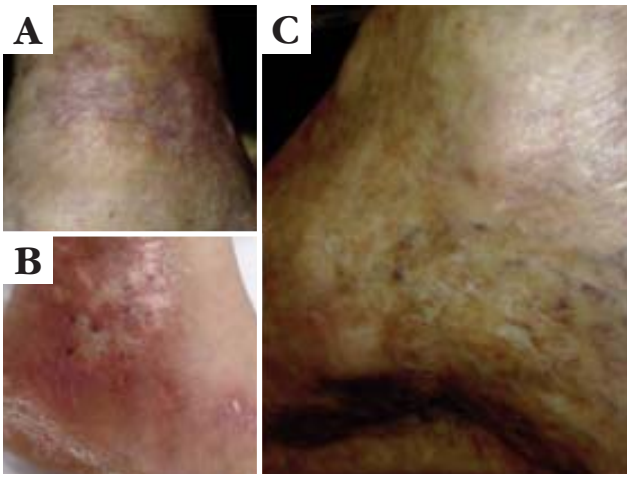

Figure 2: The ulcers become chronic ulcers that heal with an atrophic whitish, stellate or reticulated aspect (A, B and C), resulting in the classic aspect of "White Atrophy" (*atrophie blanche*). Many of these scars are surrounded by punctate telangiectasias and hemosiderosis (copper-hued)

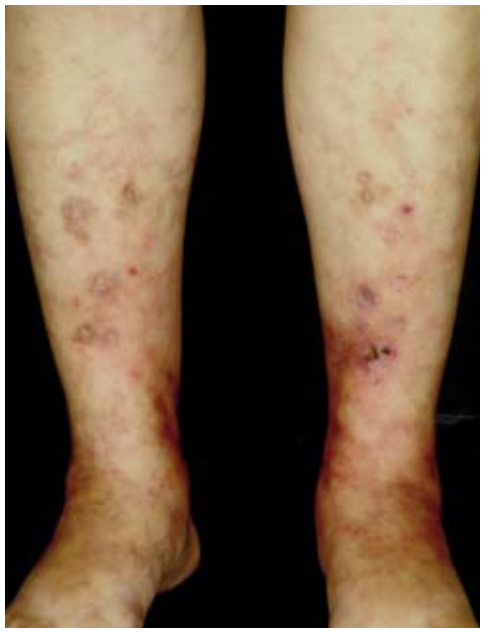

Figure 3: Livedoid vasculopathy. Observe erythematous-violaceous livedo racemosa on the legs

thrombosis a form of located venous thromboembolism, i.e., a multigenic and multifactorial disease. [9] However, its etiopathogenesis has not been fully established yet; thus, many cases remain idiopathic. Disorders related to hypercoagulable states (thrombophilias and/or autoimmune diseases are the conditions most frequently associated with LV.

In general, the three main factors that predispose to thrombosis are: endothelial damage, changes in the blood flow and blood disorders leading to hypercoagulability. [11] Indeed, reports linking Milian's white atrophy (MWA) to several clinical conditions are found in the literature. These conditions may not seem to be connected to each other at first, but when examined more closely, will be directly or indirectly related to increased risk of thrombosis.

Among the diseases that cause *endothelial damage* already listed as a cause of MWA are the following: hyperhomocysteinemia and autoimmune diseases such as SLE, scleroderma, mixed connective tissue disease, polyarteritis nodosa (PAN) and rheumatoid arthritis. [9,12-16] Changes in the blood flow not only include venous insufficiency, but also diseases that lead to hyperviscosity syndrome such as chronic myelogenous leukemia, cryoglobulinemia and heavy chain disease. [9,17]

Hypercoagulable *states* are rare situations and still partially unknown. They are currently classified as hereditary - which include genetic defects of the coagulation cascade and of fibrinolysis - and acquired. Some examples of hereditary thrombophilias are deficiencies of natural anticoagulants (antithrombin, protein C, protein S and protein Z), prothrombin mutation, factor V (Leiden) mutation, hyperhomocysteinemia (due to genetic enzyme defect) and changes in the plasma levels of coagulation factors (VIII, IX and XI), in addition to deficiencies of the fibrinolytic system (Figure 4). [8,18] Other associations related to the etiopathogenesis of LV are the presence of high levels of plasminogen activator inhibitor-1 (PAI-1) and increased levels of lipoprotein(a). [19,20] Table 1 summarizes possible etiopathogenic associations in LV.

Regardless of the etiology involved in LV, the pathogenic changes occur in the dermis, in contrast to hypodermitis, in which the pathogenic substrate is located in the subcutaneous tissue. [21]

In LV, there are no signs of true vasculitis in the form of leukocyte infiltrate on vessel walls. [21] However, the partial pressure of oxygen in these areas is largely reduced, and painful ulcerations resistant to drug therapy develop quickly. [21,22] One of the possible causes of LV is the presence of reduced fibrinolytic activity in the blood of these patients, with reduced release of tissue plasminogen activator from vessel walls (Figure 4). [19,23-25] These patients' platelets also demonstrate increased aggregation activity. [21] The levels of fibrinopeptide A, which are involved in the formation of fibrin polymers in activity, characterizing a thrombogenic state, may also be elevated (Figure 5). [1,26]

In some LV patients, the presence of lupus anticoagulant and/or anticardiolipin antibodies may also be demonstrated. [27,28] There are reports in the literature on LV associated with recurrent thrombosis in patients with SLE, possibly characterizing seronegative antiphospholipid syndrome. [29] These antiphospholipid antibodies determine an imbalance in the

Table 1: Etiopathogenic associations in livedoid vasculopathy

Chronic Venous Disease
Autoimmune Connective Tissue Disease
• Systemic Lupus Erythematosus
• Scleroderma
• Rheumatoid Arthritis
• Mixed Connective Tissue Disease
Inherited Thrombophilias:
• Factor V (Leiden) Mutation
• Prothrombin gene mutation
• Mutation in the tissue plasminogen activator inhibitor-1promoter
• Mutation of methylenetetrahydrofolate reductase (MTHFR)
• Antithrombin Deficiency
• Protein C Deficiency
• Protein S Deficiency
• Increased lipoprotein (a)
Acquired thrombophilias:
• Antiphospholipid syndrome and/or antibodies
• Cryoglobulins
• Cryofibrinogenemia
• Increased Homocysteine
Hematologic Neoplasms
Solid Organ Neoplasms
Idiopathic

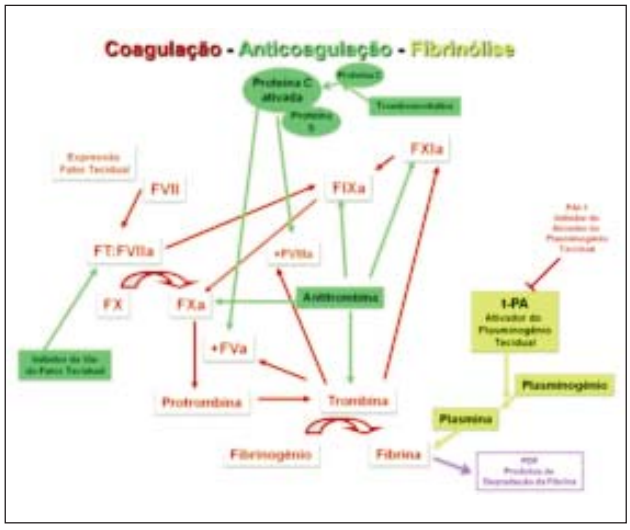

Figure 4: System of coagulation, natural anticoagulation and fibrinolysis. **Coagulation:** after vessel wall damage, the coagulation system produces a hemostatic plug through an interaction between the sub-endothelium, platelets and plasma coagulation factors. First, tissue factor (TF) is released by the sub-endothelium initiating clotting. The combination of activated factor VII (FVIIa) with TF by the Tenase complex results in the generation of FXa. 6 In the presence of FV, calcium and a phospholipid surface, the FXa converts prothrombin into thrombin. Thrombin is the key enzyme in the coagulation cascade. Thrombin acts (i) activating FV, FVII, thus increasing its own generation; (ii) cleaves fibrinopeptide A (FBA) and B from fibrinogen and forms fibrin; (iii) promotes cross-linking of fibrin by activating FXII; and (iv) acts as a potent activator of platelets. An alternative pathway of the coagulation cascade is triggered by activation of contact factors (FXII, FXI, prekallikrein, high-molecular-weight kininogen). Legend: TF, tissue factor. Anticoagulation: thrombin inhibitors are classified into direct and indirect. Direct inhibitors are antithrombin (AT), a2 - macroglobulin (a2M) and heparin cofactor II (HCII). AT and HCII mediate thrombin inhibition and are accelerated by endrogenous glycosaminoglycans and exogenous heparin. Indirect thrombin inhibitors are protein C (PC), protein S (PS) and tissue factor pathway inhibitor. The free thrombin becomes partly bound to a receptor in the endothelial cell: thrombomodulin (TM). 4 The thrombin-thrombomodulin complex cannot cleave fibrinogen anymore and no longer activates FV, FVIII and platelets. In addition, the thrombin-TM complex inhibits clotting formation through protein C (PC), forming the activated PC (APC). APC enzymatically actives FVa and FVIIIa through cleavage. APC activity is strongly enhanced by its cofactor: protein S (PS). An indirect mechanism to regulate thrombin activation is TPFI. 4 TPFI forms a complex with FXa, which inhibits FVIIa, thus inhibiting generation of thrombin. The third indirect mechanism for inhibition of thrombin is the binding of thrombin to fibrinogen clot, which results in considerable reduction in the rate of cleavage of fibrinogen

fibrinolytic activity, thus favoring thrombosis. [21]

Among the several reported associations between LV and hypercoagulable states are the following: protein C deficiency, factor V (Leiden) mutation, prothrombin gene mutation, hyperhomocysteinemia, increased levels of lipoprotein(a) and antithrombin deficiency. [8,9, 14, 20,30-36]

Consequently, given the heterogeneity of the etiopathogenic factors clinically involved in LV, we propose to classify it according to its etiopathogenesis into primary (idiopathic) or secondary to a known event or condition, with the latter being subdivided into four groups: (i) endothelial damage, (ii) changes in blood flow, (iii) states related to thrombophilias, and (iv) mixed etiopathogenesis.

The literature indexed in Medline (PubMed) from 1980 to October 2010 gathers 35 papers which include case reports or series of patients with LV associated with conditions of hypercoagulability (acquired or inherited thrombophilia) (Table 2). [8,12-14,19-20,28-33,35-57]

Histopathological findings

Some authors suggest that the clinical presentation of LV is so characteristic that there would be no need of performing a histopathological examination to diagnose the disease and that biopsy could lead to ulceration that is difficult to heal. [17] However, we disagree with this point of view due to the large differential diagnosis involved in the disease as well as to the fact that biopsy only caused difficult-to-heal ulcers among our patients on few occasions. [8,9, 58]

The initial challenge in the histopathological diagnosis of LV is to obtain an adequate skin sample, which represents from the epidermis to the dermo-

Table 2: Publications on Livedoid vasculopathy associated with hypercoagulable conditions (thrombophilia) retrieved from the literature indexed in Medline (Pubmed) from 1980 to October 2010

Author	Year	Number of cases	Detected Thrombophilia
Goerge et al.[20]	2010	1	Increased levels of (apo)Lipoprotein (a)
Tabata et al.[58]	2010	1	IgM anti-phosphatidylserine-prothrombin complex antibody (antiphospholipid antibody)
Sopeña et al. [29]	2010	1	Seronegative antiphospholipid syndrome in a patient with SLE
Di Giacomo et al.[8]	2010	34	A prospective study. Eighteen patients (52%) with thrombophilia: Antiphospholipid antibodies in 6 patients (17.64%); heterozygous factor V (Leiden) mutation in 6 patients (17.64%); protein C and/or S deficiency in 3 patients (8.82%); hyperhomocysteinemia in 2 patients (5.88%), one with MTHFR mutation and the other with associated factor V (Leiden) mutation; prothrombin (G20210A) gene mutation in one patient; elevated levels of fibrinogen in one patient and association between prothrombin (G20210A) gene mutation and IgM anticardiolipin antibody.
Osada et al.[57]	2010	1	IgM and IgG anticardiolipin antibodies
Antunes et al.[56]	2010	1	Prothrombin (G20210A) gene mutation and high levels of tissue plasminogen activator inhibitor type 1 (PAI-1), resulting from PAI-1 4g/4G promoter homozygous polymorphism
Tsai et al.55 *	2009		MTHFR gene polymorphism
Kavala et al.[54]	2009	1	Factor V (Leiden) mutation
Irani-Hakime et al.[53]	2008	1	Factor V (Leiden) mutation associated with prothrombin (G20210A) gene mutation and homozygous MTHFR (C677T) mutation with hyperhomocysteinemia
Davis & Wysokinski[52]	2008	1	Factor V (Leiden) mutation associated with prothrombin (G20210A) gene mutation
Anavekar & Kelly[51]	2007	1	Heterozygous prothrombin (G20210A) gene mutation
Kawakami et al.[50]	2007	1	Essential cryoglobulinemia
Cardoso et al. [49]	2007	1	Homozygous MTHFR (C677T) mutation without hyperhomocysteinemia and Sjogren's Syndrome
Deng et al.[19]	2006	1	Prothrombin (G20210A) gene mutation and high levels of tissue plasminogen activator inhibitor type 1 (PAI-1), resulting from PAI-1 4g/4G promoter homozygous polymorphism
Hairston et al.[32]	2006	45	A retrospective study. Twenty-one patients (46.6%) with thrombophilia: Heterozygous factor V (Leiden) mutation in 2 of 9 patients; Protein C and/or S deficiency in 2 of 15 patients; prothrombin (G20210A) gene mutation in one of 12 patients; homocysteine increase in 3 of 21 patients; anticardiolipin antibodies in 8 of 28 patients and lupus anticoagulant in 5 of 28 patients
Rampf et al.[47]	2006	1	Homozygous MTHFR (C677T) mutation without hyperhomocysteinemia
Amato et al.[46]	2006	1	Increased levels of fibrinogen
Meiss et al.[45]	2006	1	Hyperhomocysteinemia resulting from renal failure
Juan et al. [44]	2006	12	Three patients with cryoglobulinemia
Browing et al.[12]	2006	1	Cryofibrinogenemia and hyperhomocysteinemia
Lewerenz et al.[43]	2004	1	Heterozygous factor V (Leiden) mutation and sticky platelet syndrome
Gotlib et al.[33]	2003	1	Mutant prothrombin gene
Hairston et al.[42]	2003	2	One of the patients with factor V (Leiden) mutation
Hegemann et al.[35]	2002	2	Antithrombin deficiency
Calamia et al.[41]	2002	1	Factor V (Leiden) mutation
Cocuroccia et al.[13]	2002	2	Factor V (Leiden) mutation (1) Hyperhomocysteinemia (1)
Magy et al.[40]	2002	1	Heterozygous Factor V (Leiden) mutation and Lupus anticoagulant
Tran et al.[36]	2001	7	Antiphospholipid antibodies (3); platelet hyperaggregability (1); cryofibrinogen (1); decreased antithrombin activity (1); factor V (Leiden) mutation (1)
Boyvat et al.[22]	2000	1	Heterozygous Protein C Deficiency
Grasland et al.[28]	2000	1	Anticardiolipin antibodies
Biedermann et al.[31]	2000	1	Factor V (Leiden) mutation
Acland et al.[39]	1999	4	Antiphospholipid syndrome
Gibson et al.[14]	1999	*	Hyperhomocysteinemia
Wakelin et al.[38]	1998	1	Anticardiolipin antibodies
Klein & Pittelkow[23]	1992	6	Anticardiolipin antibodies, increased levels of tissue plasminogen activator inhibitor (PAI-1) and decreased levels of tissue plasminogen activator (t-PA)

** Case-control study*

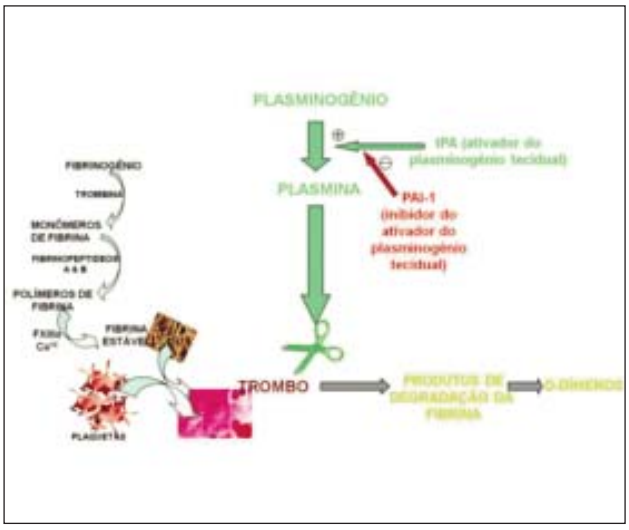

Figure 5: Fibrinolytic pathway. Tissue plasminogen activator (t-PA) converts plasminogen into plasmin, which cleaves the clot (thrombus, formed from fibrin combined to platelets), generating fibrin degradation products (FDP) and d-dimers. Fibrinolysis may be inhibited by the activity of tissue plasminogen activator inhibitor (PAI-1)

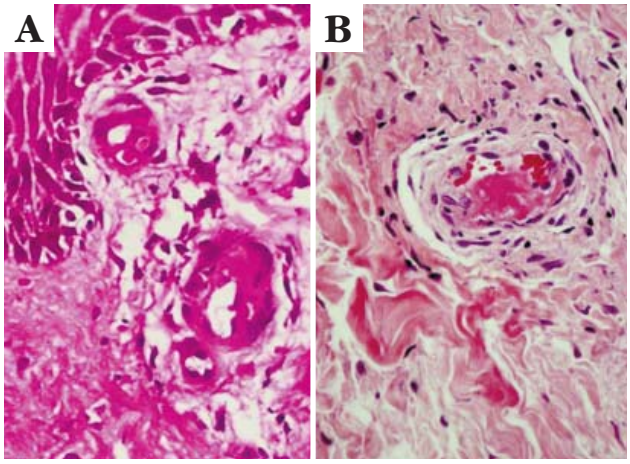

Figure 6: In (A), we observe papillary dermis vessels occluded by thrombi and hyalinized wall, in addition to perivascular edema (HE, 400x). In image (B), the occluded vessel shows fibrin and red blood cells in the thrombus, with slight perivascular lymphomononuclear infiltration (HE, 400x)

hypodermic junction. Generally, vascular involvement in LV occurs in the mid and superficial dermis, and sometimes in the deep dermis. However, representation of the dermo-hypodermal junction is necessary, since there are situations in which the lesions clinically present as LV, but represent a morphological manifestation of cutaneous polyarteritis nodosa.

Mimouri et al. reported 29 cases diagnosed as LV, but six of them represented underlying cutaneous polyarteritis nodosa, and four of them presented mononeuritis multiplex. [59] In a histopathological reevaluation of deep biopsies, the authors observed the presence of necrotizing vasculitis of medium-caliber vessels in the reticular dermis and hypodermis, whereas there were only thrombosed vessels in the superficial dermis, without inflammation and with typical characteristics of LV.

Generally, the histopathological findings of LV are characterized by occlusion of dermal blood vessels due to intravascular fibrin deposition and thrombosis, segmental hyalinization and endothelial proliferation. There is perivascular lymphocytic infiltration, usually at a minimum degree. [34] Thus, the following aspects are cardinal histopathological findings of LV: deposition of fibrinoid material in the vascular lumen, hyalinization of the vessel wall, tissue infarctions and no true vasculitis (Figure 6). [21] Direct immunofluorescence usually demonstrates deposition of immunoglobulin, fibrin and complement components. [34] Khenifer et al. suggest that the DIF findings are not specific to LV. [34]

According to Hesse & Kutzner, histopathology of LV can be observed in various evolutionary stages: [21]

(i) Initial stage. At this point, hyaline thrombus is formed in the lumen of small vessels of the superficial dermis and sometimes in the vessels of the plexus of the mid dermis. [37] The vessels of the vascular plexus of the deep dermis are involved only in rare occasions. [60,61] In addition to the presence of fibrinoid thrombus in the vascular lumen and sometimes the presence of fibrin on the vessel wall, in some cases, we can observe this fibrinoid material deposited in the perivascular stroma, which results in the classical clinical manifestation of "fibrinoid thrombus and fibrinoid rings" in the region of the superficial dermal vascular plexus. [21] This fibrinoid material can be clearly visualized through the PAS histochemical technique. [21]

In addition to these angiocentric findings, most cases present with overlying ulceration (infarction) of the epidermis and adjacent superficial dermis, even in early stages. It is sometimes accompanied by parakeratosis and marked atrophy of the surrounding epidermis. [21] The only inflammatory change is represented by the presence of a discrete perivascular lymphocytic infiltrate and no signs of leukocytoclastic vasculitis. [21] The criteria for diagnosis of lymphocytic vasculitis are not met. [21,62]

Neutrophils are occasionally found in the area of ulceration (infarction), apparently as an expression of the necrotizing ulcerative process (secondary phenomenon). [21] Extravasation of red blood cells in the superficial dermis completes the histopathological manifestation of LV. [21]

(ii) Intermediate stage. This stage is characterized by the presence of vessels with hyalinized and thickened walls in the superficial and mid dermis, sometimes with secondary endothelial proliferation. [21]

Moreover, the fibrinoid material is also present in the lumen and on the vessel wall, which has already been observed in an early stage of the disease. [21] It should be noted that these fibrinoid deposits (in the lumen and on walls) are significant for the diagnosis of LV and occur at all stages. [21] It is important to note that these fibrinoid deposits should not be confused with an analogous secondary phenomenon that occurs in almost all common ulceration. [21] This detail emphasizes the need for biopsy of lesions outside the ulcerated area, especially focusing on macular or papular erythematous-purpuric lesions not yet ulcerated.

Stasis ulcers without LV exhibit dilated, elongated and twisted capillaries and only localized and circumscribed loss of capillaries. [21] In this situation, the capillaries around the ulcer are proliferated. [21]

Direct immunofluorescence usually demonstrates deposition of immunoglobulin, fibrin and complement components. [34] There is deposition of fibrin on the vessel walls in the initial stages, and deposition of immunoglobulins and complement is detected in later stages. [1,58,63,64] Table 3 shows a series of cases of LV found in the literature review in which DIF was performed. [34,63-67] Maessen-Visch et al. and Khenifer et al. suggest that the findings on LV observed in DIF are not specific. [17,34] Some authors have interpreted the frequent finding of IgM in DIF studies on LV as a consequence of the sequestration of large complexes of immunoglobulin M, which has very high molecular weight, by deposits of fibrin in damaged vessels. [65]

Therefore, the histopathological findings in LV allow us to better classify it as *vasculopathy* instead of immune-complex-mediated necrotizing vasculitis due to: (i) absence of neutrophilic polymorphonuclear leukocytes and nuclear fragmentation in the area around dermal vessels early in the process; (ii) no permeation of the vessel wall by leukocytes; (iii) fibrin deposition and hyalinization of the vessel wall; (iv) normal serum levels of the complement in most patients and absence of detectable circulating immune complexes. [26]

Nonetheless, according to some authors, the term "Livedoid Vasculopathy" remains not completely appropriate. [67] Winkelmann et al. in 1974 and later Su & Winkelmann in 1980 proposed in a review that tissue hemosiderosis in patients with LV produce a macule described as "pseudo livedo". [7,68] Thus, there are patients who present with hemosiderosis and livedo racemosa while others do not. This raises a semantics discussion around the term "livedoid" assigned to the condition and makes it still very debatable. [45] In our viewpoint, the term livedoid alludes to its similarity with livedo, enabling it to be used, since most cases of LV present with either livedo racemosa or residual pigmentation similar to livedo .

DIAGNOSIS

Accurate diagnosis of LV requires accurate data regarding the patient's medical history, physical examination, laboratory parameters and histopathology. [32] Differential diagnosis is especially made with cutaneous small vessel vasculitis (leukocytoclastic vasculitis) and cutaneous polyarteritis nodosa (especially when there are symptoms of mononeuritis multiplex), in addition to antiphospholipid syndrome, chronic venous stasis, pyoderma gangrenosum, factitious dermatitis, pseudo-Kaposi sarcoma and Degos disease. [9] Callen proposed that all conditions that may determine reticulated punched-out ulcerations on the legs that are difficult to heal, and which can cause whitish stellate scars, should be excluded (Table 4). [69]

Is should be noted that the presence of Milian's white atrophy-like scars (*atrophie blanche*) is not exclusive to the final stage of LV. It is present in other conditions such as SLE, scleroderma, Degos disease and more frequently in chronic venous insufficiency (9% to 38% of the patients), with or without ulceration, thus simply representing scar morphology resulting from various types of injury and not indicative of a nosological entity. [17]

Once the required differential diagnoses have been carried out and the presence of LV is confirmed, an accurate laboratory evaluation aimed at determining the presence of abnormalities suggestive of autoimmune connective tissue diseases, congenital and acquired thrombophilias, paraproteinemia, serology for hepatitis B and C and HIV test must be performed. Particular attention should be given to the quality of the skin biopsy, since LV is defined based on clinical and histopathological findings. [32] It is advisable to avoid obtaining tissue samples from the basis of the ulcer, giving preference to its immediate borders. If this precept is not followed, only representations of granulation tissue and/or inflammation secondary to tissue repair may be obtained. [32] Given the focal and segmental nature of the vascular changes in LV, multiple biopsies may be required to represent it properly. [32] The most appropriate tests for the diagnostic investigation of LV are summarized in Table 5. With the continued evolution of laboratorial propedeutics of coagulation disorders, it seems that the forms of LV formerly considered "idiopathic" will become less and less common. [32]

TREATMENT

The therapeutic approach of LV is varied[21]. Its recurrent nature makes it difficult to evaluate the efficacy of a particular drug or measure, since improvements of the condition may be due to the natural course of the disease. However, a parameter that may assist in the therapeutic evaluation of these patients is

Table 3: Different studies involving the use of direct immunofluorescence in cases of livedoid vasculopathy, retrieved from the literature indexed in Medline (Pubmed)

Year of Publication	Authors	DIF Findings	Patients (no.)
2010	Hisao and Wu43	100% positive; homogeneous pattern; fibrinogen > C3 > IgM >IgA > IgG	27
2006	Hairston et al.34	86.1% positive; C3 > IgM > IgA > IgG	42
1991	Yang et al.44	80% positive; IgM > C3 > IgA > IgG	10
1983	Schornik et al42	Lesions in early stage of development: fibrin; Lesions in later stages of development: IgM, IgG, C3 and fibrin within and on vessel walls	12
1975	Schroeter et al.41	100% positive; IgM > C3 > IgG >IgA	15

the symptom of pain.

Pain in LV has an ischemic character (focal cutaneous infarction), as demonstrated by Hairston et al. through the measurement of skin oxygen tension ($TcPO_2$), which showed to be reduced in their patients. Thus, pain is usually present in all individuals, strongly affecting their social and work activities and eventually drifting them away even from family life. [32] George et al. used a visual scale for assessing pain in a child (to quantify improvement of LV in a less subjective way) undergoing anticoagulation treatment based on low molecular weight heparin. [20] The method was relevant and had a course parallel to the healing of lesions. [20]

It is not uncommon to see patients whose LV is refractory to treatment, especially in cases with numerous extensive ulcerations that are intensely painful and difficult to heal. [42]

Several therapeutic approaches have been employed with varying degrees of success. [17] The use of topical, systemic and intralesional corticosteroids has shown little or no efficacy. [17] However, all forms of treatment proposed for LV are based on reports of isolated cases or case series. Unfortunately, there are no good clinical studies (prospective, randomized, placebo-controlled) that meet Cochrane's criteria available. [70] Probably, this is partly due to the relative rarity of the condition, coupled with the fact that it is a debilitating disease of high morbidity, hampering such studies difficult from an ethical point of view, especially the use of placebo.

Since there is potential involvement of thrombogenic mechanisms or deficiency of the fibrinolytic process, the various therapies aim to modulate or interfere with microcirculatory hemostatic disorders. [17,21,32,42] The main groups of drugs used in LV are:

(i) Drugs stimulating endogenous fibrinolytic activity:

Initially, a combination of phenformin (antidiabetic) and ethylestrenol, which increased endogenous blood fibrinolytic activity by increasing the activity of plasminogen enzymes. [17] Phenformin was withdrawn from the U.S. market due to its adverse effects, and ethylestrenol is an anabolic steroid with some progesterone and androgen activity whose use in Brazil is subject to special control. [71] Both drugs are not effective when used alone. Another androgenic steroid drug with fibrinolytic activity used in LV is danazol, 200 mg orally a day. [38,72-74]

Tissue plasminogen activator inhibitor (PAI-1) is an important inhibitor of the fibrinolytic system. [19] It consists of a single-chain glycoprotein synthesized in the liver, adipose tissue and endothelial cells. [19] PAI-1 is the primary inhibitor of both t-PA and urokinase-type plasminogen activator. [19] Synthesis of PAI-1 is induced under the regulation of mediators such as endotoxin, IL-1, TNF-α, TGF-2 and lipids. [72] The discovery of genetic polymorphisms of the PAI-1 promoter clarified more information about its function. [19] The PAI-1 gene has several polymorphic loci. [19] The most important polymorphism is the 4G/5G insertion-deletion of 675 base pairs at the beginning of the promoter, which affects the binding of nuclear proteins involved in gene transcription regulation. [19] The 4G allele appears to bind only the enhancer; thus, the 4G/4G genotype determines an increased synthesis of PAI-1, while the 5G allele binds both the enhancer and the suppressor, resulting in a low level of transcription. [19] The presence of PAI-1 4G/4G genotype confers an increase about 25% higher in plasma levels in relation to the 5G/5G genotype, thus contributing to reduction of fibrinolysis. [19]

Thus, recombinant tissue plasminogen activator (rt-PA) (Alteplase - Actilyse©) has been currently used at a low dose. [19, 23] Klein & Pittelkow used intravenous rt-PA at a dose of 10 mg every 4 hours for 14 days. [37] Deng et al. used intravenous rt-PA at a dose of 10 mg daily for two weeks, but associated with subcutaneous heparin 5000 IU every 12 hours and ASA 81mg/day. [19]

CHART 4: Differential diagnosis of reticulated leg ulcers

Disease or condition	Suggestions for diagnosis
VASCULOPATHIES	
Livedoid vasculitis	Medical history, physical examination and histopathology
Antiphospholipid syndrome	IgG and IgM anticardiolipin antibodies, lupus anticoagulant and anti-β2-glicoprotein I antibodies. Recurrent thrombosis; obstetric history of fetal loss.
Paraproteinemia:	
• Cryoglobulinemia, • Cryoglobulins • Cryofibrinogenemia, • Macroglobulinemia, • Hyperglobulinemia	Determination of immunoglobulin, kappa and lambda chains, cryoglobulins, cold agglutinins and cryofibrinogen
Genetic conditions that predispose to thrombosis (inherited thrombophilia):	
• Factor V (Leiden) Mutation	Gene amplification by PCR, followed by analysis of restriction fragment length polymorphism (PCR - RFLP) to find R506Q mutation of the Factor V gene
• Protein Z, protein C and/or S deficiency	Search for total and free proteins C and S
• Hyperhomocysteinemia	Plasma levels of homocysteine and related metabolites are high (above 13.9 micro mol per liter). PCR search for MTHFR C677T and A1298C mutations
• Prothrombin gene mutation	PCR-RFLP to find prothrombin G2021A gene mutation (Factor F2)
• Mutation in the promoter of tissue plasminogen activator inhibitor (PAI-1)	Genetic Polymorphism of Plasminogen Activator Inhibitor type 1 (PAI-1) by PCR. 4G/5G polymorphism was associated with PAI-1 plasma concentrations. The 4G allele associates with significantly higher PAI-1 concentrations than the 5G allele, especially in the presence of elevated triglyceride levels.
• Increased (apo)lipoprotein (a)	Determination of serum (apo)Lipoprotein (a)
VASCULITIS	
Cutaneous Polyarteritis Nodosa *Systemic Polyarteritis Nodosa*	Livedo racemosa, subcutaneous nodules on the legs, mononeuritis multiplex, ulcerations Idem + hypertension and renal failure
Microscopic polyangiitis	Palpable purpura, retiform purpura-like lesions and reticulated ulcerations, mononeuritis multiplex, p-ANCA positive, pulmonary and renal disease
Granulomatous vasculitis	Palpable purpura, retiform purpura-like lesions and reticulated ulcerations, p-ANCA or c-ANCA positive, pulmonary and renal disease
Small Vessel Vasculitis:	Palpable purpura, cryoglobulins present
-Essential mixed cryoglobulinemia	Palpable purpura, serum complement consumption, ANA,
-Autoimmune Connective Tissue Disease	positive anti-DNA, renal disorders, etc.
Chronic Venous Insufficiency	Varicose veins, ochre dermatitis, edema of the lower limbs, abnormal venous Doppler ultrasound
Peripheral Arterial Disease	Pale skin, claudication, painful ulcers, abnormal artery Doppler ultrasound
Ulcerations caused by the use of Hydroxyurea	Use of hydroxyurea (e.g.: Polycythemia Vera)

Table 5: Tests for the diagnostic investigation of Livedoid vasculopathy

Diagnostic approach	Complementary exams
Autoimmune Connective Tissue Diseases	ANA, ANCA, anti-DNA double helix, Anti-Ro, anti-La, RF, C3, C4, CH50, complete blood count, urinalysis, and physical examination.
Paraproteinemia:	Determination of Immunoglobulins (IgM, IgG, IgA and IgE), protein electrophoresis, immunofixation, determination of kappa and lambda chains and physical examination.
Neoplasms	DHL, complete blood count, anamnesis of several tracts and physical examination.
Peripheral vascular disease	Pulse examination and artery and venous Doppler ultrasound study
Thrombophilias	**I. Acquired thrombophilias:** • Anticardiolipin antibodies (IgM and IgG) • Lupus anticoagulant • Anti-β2-glicoprotein I antibodies • Cryoglobulins, cryoagglutinins, cryofibrinogen • Homocysteine (folic acid, vitamin B12 and B6 deficiency, chronic renal failure, pernicious anemia, use of folic acid antagonists, vitamin B6 antagonists, old age) **II. Congenital thrombophilias:** • Factor V (Leiden) Mutation • Prothrombin Mutation • MTHFR mutation, hyperhomocysteinemia due to a defect in cystathionine-β-synthase and methionine synthase • Polymorphism in the promoter of the tissue plasminogen activator inhibitor (PAI-1) • Serum levels of tissue plasminogen activator (t-PA) and tissue plasminogen activator inhibitor (PAI-1) • Determination of lipoprotein (a) • Determination of Antithrombin • Determination of Protein C and Protein S **III. Of uncertain cause:** • Fibrinopeptide A Levels • Determination of D-dimers • Platelet activity

(ii) Drugs that inhibit thrombus formation (antiplatelet):

Drugs inhibiting prostaglandin synthesis, which modulate platelet aggregation and thus inhibit it, are used in the treatment of LV: acetylsalicylic acid, dipyridamole, cilostazol or the group of thienopyridines (clopidogrel, ticlopidine hydrochloride, associated or not with ASA). [17] Osada et al. used sarpogrelate hydrochloride, an antagonist of the 5-hydroxytryptamine$_{(2A)}$ receptor ($5HT_{2A}$) and consequently of serotonin. [56] Sarpogrelate has an antiplatelet and antivasoconstrictor action and was used at daily doses of 300mg orally. However, the patient presented peripheral neuropathy during treatment, which only improved with the introduction of warfarin. [56]

(iii) Vasodilator drugs:

Nifedipine, Cilostazol (phosphodiesterase III inhibitor) and nicotinic acid have been employed. [17]

(iv) Hemorheologic drugs:

These drugs aim to reduce blood viscosity, increase flexibility of red blood cells and thus increase inflow circulation. Oral pentoxifylline, 400 mg every 8 hours, and buflomedil hydrochloride are employed with this purpose. [75] Buflomedil has an inhibitory effect on platelet aggregation and improves deformability of erythrocytes with abnormal flowability. Although the mechanism by which buflomedil induces these effects has not yet been defined, early data suggest that a non-specific and weak antagonistic effect of calcium ions (*in vitro only)* and a non-specific blocking effect of alpha-receptors are partly involved. The recommended oral dose is 150 mg three to four times daily or 300 mg twice a day.

(v) Modulators of lymphocyte response:

Systemic phototherapy with PUVA (UVA + oral 8-methoxypsoralen) has been used by some authors. [76-78] PUVA was introduced with a UVA dose of 4J/cm^2, applied two to three times a week and with increments of 0.5 to 1J/cm^2 each treatment, as tolerated. [77]

(vi) Therapies of still poorly understood mechanisms:

Other drugs used in case reports were intravenous immunoglobulin, cyclosporine, hyperbaric oxygen therapy and intravenous iloprost. [8,40,44,79-83]

Intravenous immunoglobulin (IVIG) seems to be an exceptional therapeutic alternative due to its high cost. It was used at a dose of 0.5 g/kg/day for 3 consecutive days. [81] In dermatology, IVIG has been used in several autoimmune diseases, especially bullous diseases such as pemphigus vulgaris and bullous pemphigoid and also in collagen diseases such as vasculitis. [81,84] Its form of action is not fully understood. IVIG is generally well tolerated. Adverse effects such as headache, chills, fever, nausea, vomiting, dyspnea and tachycardia occur in less than 5% of the patients treated. [81] Episodes of anaphylactic reaction, renal failure and hemolytic anemia are rare. [81]

Cyclosporin A (CsA) was used by Leclerc et al. in the treatment of LV in five patients with good results. Its mechanism of action is still unknown. [82] It is known that CsA acts as an immunosuppressant of lymphocyte activity; however, it seems that lymphocytes do not play an important role in the pathogenesis of LV. Tissue factor (TF) is a vital component in triggering coagulation cascades. Studies have shown that CsA inhibits the expression of TF in monocytes by inhibiting TF gene transcription, which could contribute to its beneficial effect in LV. [85-87] In the Dermatology Clinic of HC-FMUSP, good results have also been obtained with the use of CsA at doses similar to those used in psoriasis (3 to 5mg/kg/day). However, it has been observed that suspension of the drug frequently results in recurrence of the disease. Renal toxicity and the immunosuppressive effects of the drug do not allow for its use on an uninterrupted basis in the treatment of LV. However, it may be used as rescue treatment when other treatment forms have failed.

Hyperbaric oxygen therapy (HBOT) involves inspiring a fraction of oxygen close to one (pure *oxygen* or *100% oxygen*) in an environment with pressure (usually two to three times) higher than the atmospheric pressure at sea level. [88] This increased pressure will result in significant increased arterial and tissue oxygen tension (close to 2000 mmHg and 400 mmHg, respectively), which explains most of the physiological and therapeutic effects of hyperbaric oxygen. [88] In accordance with *Henry*'s law, by breathing pure oxygen in a hyperbaric environment, it is possible to observe an increase in arterial oxygen tension, which may exceed 2000 mmHg at an environmental value of three atmosphere absolute (ATA). The amount of oxygen dissolved and transported by the plasma, which is minimal at atmospheric pressure, increases more than 22 times. [88] Thus, if we compute the plasma oxygen content (oxygen dissolved in plasma), we find that the amount of oxygen that the plasma carries at sea level is about 0.3 ml/dl, while the oxygen dissolved is approximately 6 ml/dl at three ATA. [88] The latter figure is enough for cellular consumption at rest, without any contribution from oxygen bound to hemoglobin. [88]

In damaged hypoxic tissues, HBO stimulates the formation of collagen matrix, essential for angiogenesis and wound healing, as it contributes to the reversal of hypoxia. [88] It is known that the hyperoxia/normoxia alternation is a significant angiogenic stimulus. [88] Another well-established effect of HBOT is the improvement in microvascular perfusion. [88] This effect is probably related to stimulation of nitric oxide (NO) synthesis by hyperbaric oxygen. [88] On average, treatment consists of daily sessions of 90 to 120 minutes.

We observed four patients with LV at HC-FMUSP to whom HBOT was indicated (data not yet published). During treatment, these patients underwent 20 to 25 sessions until complete healing of the lesions (Figure 7). Pain was completely relieved between the seventh and twelfth sessions. In Brazil, HBOT coverage by private health plans has been regulated by the National Health Agency for Private Health Insurance (Agência Nacional de Saúde Suplementar - ANS) through the Normative Resolution 211 of 2010. [89] However, good scientific studies are still needed to confirm the efficacy of HBOT in LV.

Tsutsui et al. demonstrated significant reduction in the expression of thrombomodulin (TM) in endothelial cells of four patients with LV. [90] Another mechanism that increases platelet aggregation is the deficient expression of thrombomodulin, which also activates protein C of the anticoagulation system. Knowing that prostaglandin I_2 (PGI_2) stimulates the expression of TM in the endothelium, the authors used beraprost sodium, an analogue of PGI_2, for the treatment of LV initially at a dose of 120 micrograms/day, intravenously, and then at a dose of 60 micrograms/day, intravenously, associated with low doses of ASA for maintenance, obtaining clinical improvement in 4 patients.

(vii) Anticoagulant drugs:

Due to the thrombogenic mechanisms potentially involved in LV, treatment options based on anticoagulant drugs have been frequently used. [8,42] Vitamin K antagonist oral anticoagulants, especially warfarin,

have been used by several authors. [8,12,19,50,51,53,56,69] The INR (*International Normalized Ratio*) is usually maintained between 1.5 and 2.0. [8,12] However, it is sometimes difficult to manage the use of oral anticoagulants, given the frequent drug interactions and the patient's diet interference (supply of vitamin K in food). This makes it hard to maintain the INR levels and leads us to reserve the use of these agents for special situations, such as for individuals with LV and recurrent episodes of thrombosis, due to genetic mutations related to thrombophilia or antiphospholipid syndrome.

When opting for the use of warfarin, the clinician should use low doses at the beginning of the treatment, not exceeding 1 to 2 mg daily, with daily slow increments of 1 to 2mg until the dose required to reach the desired INR is achieved, or associate it in the first 3 to 5 days with subcutaneous heparin. [91] This practice has been used to prevent fast consumption of vitamin K-dependent anticoagulantion proteins (protein C, S and antithrombin), which can determine the manifestation of "coumadin-induced skin necrosis," a rare adverse effect that occurs in 0.01 to 1% of the patients using these drugs. [91] Warfarin has been maintained by our group for one to two months after healing of the lesions, when it is then stopped and reintroduced if necessary, thus avoiding the risk of bleeding associated with prolonged anticoagulation. [8]

Another form of anticoagulation, to which we have given preference, is the use of subcutaneous heparin. [8] Several authors have used mini-doses of heparin or even full dose anticoagulation. [8,19-21,32,43,45,48,67,92-95]

Both unfractionated heparin *(UFH)* and low molecular weight heparins *(LMWHs)* have established employment in the prevention and treatment of venous thromboembolism (VTE) and as adjunctive therapy in atheroembolic syndromes. [96] LMWHs are replacing UFH in anticoagulation therapy due to a number of advantages, which include a more predictable pharmacokinetic profile and ease of use. [96] There are differences among the LMWHs, since they are heterogeneous compounds produced via different processes and, therefore, with different pharmacological and biochemical properties. Among the most commonly used LMWHs are enoxaparin and dalteparin.

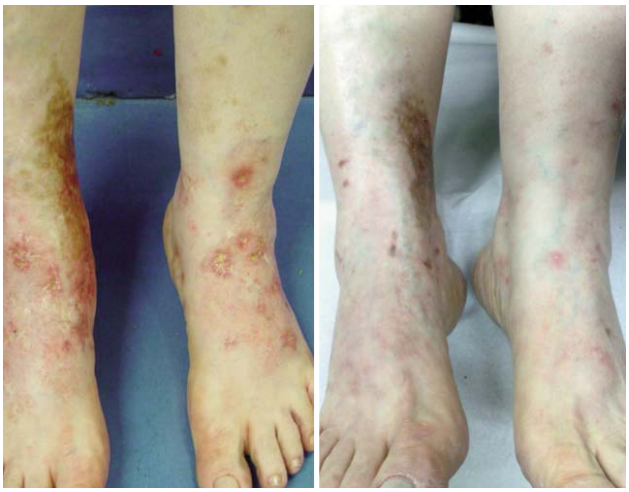

Figure 7: Patient with livedoid vasculopathy treated with hyperbaric oxygen therapy before (left) and after (right) 20 sessions

Enoxaparin has a molecular weight of 4500 daltons, with a bioavailability of 90-92% and elimination half-life of 4.5 hours. [96] The recommended prophylactic doses of enoxaparin vary from: (i) 30 mg twice daily, subcutaneously, or 40mg daily, in cases of hip surgery; (ii) 30 mg twice daily, subcutaneously, starting 12-42 hours after knee surgery; (iii) 40 mg, once daily, subcutaneously, in acutely ill patients; and (iv) 40mg once daily, 2 hours prior to abdominal surgery. [96] The recommended dose for outpatients with deep vein thrombosis, with or without pulmonary embolism, is 1mg/kg, subcutaneously, twice a day, associated with warfarin. [96]

Dalteparin has a molecular weight of 6000 daltons, with a bioavailability of 87% and elimination half-life of 3 to 5 hours. [96,97] The recommended prophylactic doses of dalteparin vary as follows: (i) 5000IU, once daily, subcutaneously, in the post-operative period in cases of hip surgery; (ii) 2500IU or 5000IU, once daily, subcutaneously, 1 to 2 hours before abdominal surgery; and (iii) 5000IU, once daily, subcutaneously, in acutely ill patients; and (iv) 200IU/kg (max. 18000IU), once daily, subcutaneously, for a month, and then 150IU/kg (max. 18000IU), once daily, subcutaneously, for 5 months for secondary prophylaxis in patients with cancer under treatment. [96] The recommended dose for outpatients with deep vein thrombosis, with or without pulmonary embolism, is 1mg/kg, subcutaneously, twice a day, associated with warfarin. [96,97]

The most appropriate recommended doses of UFHs and LWMHs for treatment of LV have not been established yet. [8,42] Hairston et al. used enoxaparin in two patients at a dose of 2mg/kg/day and later 1mg/kg/day. [42] DiGiacomo et al. used enoxaparin doses of 40mg/daily (5 patients), dalteparin doses of 5000IU/daily (3 patients) and unfractionated heparin doses of 5000IU every 12 hours (3 patients) (Figure 8). [8] In 1991, Yang et al. treated 27 patients with Milian's white atrophy during a seven-year-observational study with unfractionated heparin at a dose of 5000 IU daily in 70% of these patients. [66] The authors found significant pain relief in these patients. [66]

In 2008, Hesse & Kutzner reported their experience in treating 22 patients with ulcerated Milian's white atrophy: 16 patients received dalteparin (2500IU) once daily for 14 days and then every two days until the ulcers were healed; four patients were treated with nadroparin (2850IU, 0.3 ml) at a dose scheme similar to that of dalteparin; two patients were treated with enoxaparin. [21] All of these doses were below the dose for prophylaxis of thrombosis. [21] The mean time of use of LWMHs in this study was about 7 weeks, and 19 out of the 22 patients had their ulcers healed and were asymptomatic after three months of treatment. [21]

Goerge et al. described a pediatric patient with LV whose only condition predisposing to thrombosis was the presence of elevated levels of lipoprotein (a) [Lp (a)]. [21] The child was treated with LWMH (enoxaparin) and showed remission of the ulcers and pain. Lp (a) competes with plasminogen, since it binds to its lysine residues blocking its fibrinolytic capacity and pericellular proteolysis. Thus, high plasma concentrations of Lp (a) may represent a potential source of antifibrinolytic activity. [98]

Heparins, particularly LMWHs, have antithrombotic effects: (i) via anti-Factor Xa effect of the coagulation cascade; (ii) by increasing fibrinolytic activity as they enhance the activity of tissue plasminogen activator (t-PA); and (iii) by releasing tissue factor pathway inhibitor (TFPI). [21] LMWHs also show anti-inflammatory effect, which is detected even with tissue levels 12 to 50 times lower. [21,98] Enoxaparin has an inhibitory action on the expression of P-selectin (CD-62P), reduces the expression of ICAM-1 in endothelial cells and decreases the expression of matrix metalloproteinases in a dose-dependent manner, thus exerting its anti-inflammatory functions. [21,99, 100]

The side effects of the use of enoxaparin are similar to those of unfractionated heparins. [43] These side effects include major and minor hemorrhagic episodes (including intracranial or retroperitoneal bleeding) and thrombocytopenia. [43] Monitoring activated partial thromboplastin time (APTT) with LWMHs is not necessary, nor is it necessary to monitor INR, as it is required with warfarin. [43] However, patients should be informed of the possibility of bleeding events while undergoing anticoagulant therapy, as well as contraindications to anticoagulation must be strictly observed prior to initiating treatment. [43] Moreover, the risk of osteoporosis must be evaluated when using heparin treatment, since this effect is the main treatment complication, thus requiring prescription of calcium dietary supplements. [43]

The Thrombosis Task Force of the British Committee for Standards in Haematology recommended that, when re-introducing the use of heparin within a period of 100 days, platelet count should be carefully monitored on the first day of use. [101] Although the concomitant use of heparin and antiplatelet agents (ASA) is to be avoided, given the possibility of increased risk of bleeding, severe symptoms of LV may justify their concomitant use. [43]

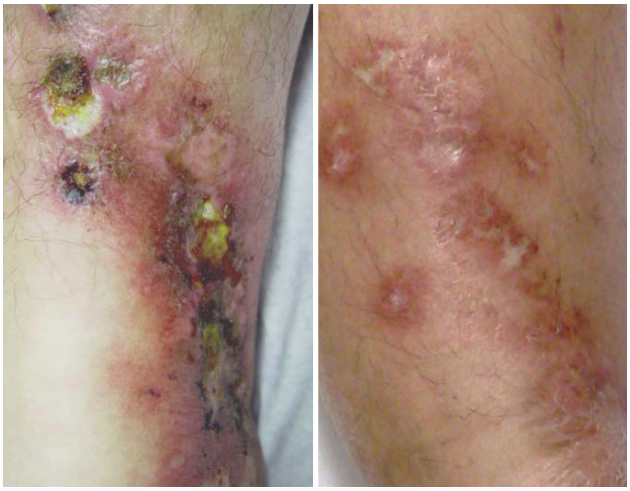

Figure 8: 35-year-old female patient with heterozygous factor V (Leiden) mutation and IgM anticardiolipin, who received subcutaneous enoxaparin 40mg every 12 hours for 5 months (see left image for before treatment and right image for after treatment), showing complete remission of pain after 3 weeks of treatment and healing of ulcers 3 months after starting using enoxaparin

Regarding the cost of treatment with heparins, especially LWMHs, it is generally high compared to other approaches such as the use of ASA combined with pentoxifylline, warfarin, vasodilators, among others. The benefits of LV treatment with LMWHs for patients with disease resistant to other approaches outweigh the costs, though, since it offers the possibility of returning to work and social activities, decreases the need for hospitalization or dressing care and improves quality of life. [21,43] However, this is a treatment whose commercial availability has not been authorized yet and which lacks evidence-based studies. [21] Nonetheless, it can be a viable therapy option in the treatment of LV, especially for treating patients with documented thrombophilia. [43]

Vitamin K antagonists (phenprocoumon, warfarin and acenocoumarol) are widely used for preventing thromboembolic disorders. These agents determine inhibition of vitamin K-dependent coagulation factors (FII, FVII, FIX and FX). [102] They are administered orally, metabolized by cytochrome P450 liver enzymes (especially those of the CYP2C9 subfamily) and excreted in bile as inactive metabolites. Despite their relatively low cost, they have disadvantages

Table 6: Literature data regarding the use of anticoagulant therapies used in Livedoid vasculopathy

Treatment		Dose and posology	Authors:	Year	Number of Patients	Presence of thrombophilia
Heparin	Unfractionated heparin	5000IU, subcutaneously, every 3 days	Jetton & Lazarus95	1983	1	ND
		5000IU, subcutaneously, every 12 hours	Heine & Davis92	1986	1	ND
		5000IU, subcutaneously, daily	Yang et al66	1991	19	ND
			Lewerenz et al43	2004	1	Sticky platelet syndrome and factor V (Leiden) mutation
		5000IU, subcutaneously, every 12 hours after use of rtPA 10mg/daily for 2 weeks	Deng et al19	2006	1	Tissue plasminogen activator inhibitor-1 (PAI-1) promoter homozygosity (4G/4G)
		5000IU, subcutaneously; 2 patients every 12 hours and 1 patient once a day	DiGiacomo et al8	2010	3	Absent
	Low molecular weight heparins (LWMHs)	Subcutaneous enoxaparin 30mg every 12 hours	Hairston et al42	2003	1	Factor V (Leiden) mutation
		Subcutaneous enoxaparin 1mg/kg every 12 hours	Hairston et al42	2003	1	Absent
			Francès & Barete93	2004	2	ND
		Subcutaneous enoxaparin (40mg/daily) + pentoxifylline and folic acid, vitamins B6 and B12	Meiss et al45	2006	1	Hyperhomocysteinemia resulting from chronic renal failure
		Subcutaneous dalteparin 2500IU/daily for 14 days and then every 2 days	Hesse & Kutzner21	2008	16	ND
		Subcutaneous nadroparin 2850IU/daily	Hesse & Kutzner21	2008	4	ND
		Enoxaparin	Hesse & Kutzner21	2008	2	ND
		Subcutaneous enoxaparin 20mg/daily. Oral methylprednisolone 32mg/daily	Cardoso et al49	2007	1	Sjögren's syndrome and MTHFR mutation with normal levels of homocysteine
		Enoxaparin	Goerge et al20	2010	1	Elevated levels of lipoprotein (a)
		Dalteparin	DiGiacomo et al8	2010	3	1 patient with IgM and IgG anticardiolipin antibodies
		Subcutaneous enoxaparin 40mg/daily	DiGiacomo et al8	2010	5	1 patient with factor V (Leiden) mutation and 1 patient with protein C and S deficiency
Warfarin			Deng et al19	2006	1	Tissue plasminogen activator inhibitor (PAI-1) promoter homozygosity (4G/4G)
			Browing & Callen12	2006	1	Cryofibrinogenemia and hyperhomocysteinemia
			Anavekar & Kelly51	2007	1	Heterozygous prothrombin gene mutation
			Davis & Wysokinski52	2008	1	Heterozygous factor V (Leiden) mutation
			Kavala et al54	2008	1	Factor V (Leiden) mutation
			Osada et al57	2010	1	Absent
			DiGiacomo et al8	2010	5	Two patients with factor V (Leiden) mutation

Legenda: ND, não detectada

which include slower onset of action, a narrow therapeutic window (bleeding complications), as well as numerous drug and food interactions. [102]

Table 6 shows the different anticoagulant therapies used in the treatment of LV, whose published articles are indexed in Medline (PubMed).

CONCLUSION

Livedoid vasculopathy remains an enigmatic condition in terms of its etiopathogenesis, but the forms formerly known as idiopathic have apparently become less and less common. The occlusive nature of cutaneous microcirculation is well defined. The association of congenital and acquired thrombophilic conditions with cases of LV, either as determinants of thrombosis or fibrinolysis deficiency, is strengthened with each new publication about LV. In the future, availability of an entire laboratory profile of thrombophilia will likely increase the findings on this association.

The challenge remains in the clinical management of these patients, who clearly suffer from pain, social withdrawal and inability to work. In our point of view, these individuals' jeopardized quality of life and their physical and moral suffering justify several of the therapeutic approaches mentioned here, even though we still lack a body of scientific evidence structured in accordance with the concept of evidence-based medicine. ❑

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