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Livedoid vasculopathy: A multidisciplinary clinical approach to diagnosis and management

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ABSTRACT

Livedoid vasculopathy (LV) is a rare, chronic, and occlusive disease of the veins supplying the upper parts of the skin. The pathogenesis of the disease is not precisely understood, and its attacks are often unpredictable but tend to worsen during the summer. LV affects women more often. This increased risk for LV in women might be related to sex-specific physiological conditions, such as pregnancy, or a higher incidence of LV-associated conditions, such as connective tissue diseases, hypercoagulable states, and venous stasis in women. The typical clinical appearance of LV consists of three main findings: livedo racemose, atrophie blanche, and skin ulcers. The purpose of this comprehensive review was to analyze LV in all aspects and mainly focus on early diagnosis for successful clinical management with a holistic and multidisciplinary approach. A detailed history, dermatological examination, and laboratory testing are essential for a diagnosis of LV. When LV is clinically suspected, a skin biopsy should be taken to confirm the diagnosis. Another critical step is to investigate the underlying associated conditions, such as connective tissue diseases, hypercoagulable states, thrombophilia, and malignancy. Unfortunately, no associated conditions can be detected in approximately 20% of all cases (idiopathic LV) despite all efforts. The diagnosis of the disease is delayed in most patients. Thus, irreversible, permanent scars appear. Early and appropriate treatment reduces pain and prevents the development of scars and other complications. Antiplatelet drugs and anticoagulants can be preferred as the first-line treatments along with general supportive measures. Other therapeutic options might be considered in unresponsive cases. Preference for refractory cases is based on availability, clinical experience, and patient-related factors (comorbidities, age, sex, and compliance). These include anabolic steroids, intravenous immunoglobulin, hyperbaric oxygen therapy, psoralen-ultraviolet A, vasodilators, fibrinolytics, immunomodulators, and immunosuppressives.

Contents

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What is known about this subject regarding women and their families?

- Livedoid vasculopathy (LV) affects women more often than men (female:male ratio ~3:2). This increased risk of LV in women might be related to sex-specific physiological conditions, such as pregnancy, or a higher incidence of LV-associated conditions, such as connective tissue diseases, hypercoagulable states, and venous stasis in women. Furthermore, various inherited coagulation abnormalities have been identified in patients with LV; thus, possible underlying genetic abnormalities must be uncovered to protect other family members.
- Disfiguring complications, especially painful ulcers and scarring, could have detrimental effects on social and personal relationships and substantially deteriorate patients' quality of life.
- The literature published to date is scarce and/or absent regarding specific considerations for women, the differences between sexes in terms of genetic susceptibility, therapeutic choices, and outcomes, as well as quality of life and long-term results.

What is new from this article as messages for women and their families?

- Significantly few high-quality studies have addressed problems regarding livedoid vasculopathy (LV) and therapeutic choices.
- Reviews and consensus papers are of utmost importance because they show the scientific gap regarding the disease and treatment for specific groups. The current review reveals an urgent need to study and identify specific approaches regarding epidemiologic differences between the sexes, underlying conditions, quality of life, management, and long-term results for LV.
- Recently, an association of LV with certain genetic variants, especially PAI-1-675 4G/5G, is highlighted.
- Anticoagulants are the most reported monotherapy recently and can be selected in patients with thrombophilia and/or without significant improvement after antiplatelet treatment. Rivaroxaban is preferred due to its advantage of oral administration and the unnecessity of international normalized ratio follow-up, which increases patient compliance.

Introduction

Livedoid vasculopathy (LV) is a rare, chronic, and recurrent thrombo-occlusive disease of the veins supplying the upper parts of the skin (Alavi et al., 2013). It has had several names due to its complicated nature, including livedo vasculitis, segmental hyalinizing vasculitis, livedo reticularis with summer ulceration, Milian white atrophy, atrophie blanche en plaque, and painful purpuric ulcers with a reticular pattern of lower extremities (or PURPLE) since its first description by Milian (1929). However, Bard and Winkelmann (1967) first used the term livedoid vasculopathy in 1967. The primary pathology is hypercoagulability, although inflammation plays a secondary role. Thus, LV is different from inflammatory vasculitis and classified as a coagulating disorder, a vasculopathy, which occurs when a thrombus forms in the arterial lumen and compromises blood flow. LV shows a chronic course with periodic and recurrent exacerbations, often affecting the legs bilaterally (Criado et al., 2011). Definite diagnosis of LV is based on clinical manifestations and histopathological findings. LV substantially affects patients' quality of life because of its recurrent clinical course, pain, and scarring.

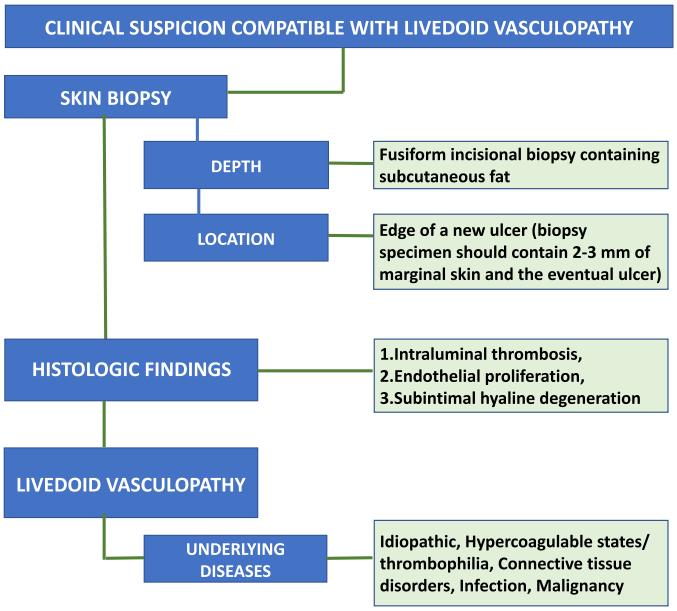

Fig. 1. Diagnostic approach to livedoid vasculopathy.

Early diagnosis and treatment before ulcer development can reduce pain and prevent the development of scarring, disfigurement, and other complications. Therefore, a multidisciplinary team approach involving professionals from pathology, rheumatology, hematology, radiology, cardiac surgery, infectious disease, and oncology is imperative for accurate diagnosis, identification of underlying conditions, and optimal treatment.

The literature published to date is scarce and/or absent regarding specific considerations for women, differences between the sexes in terms of genetic susceptibility, therapeutic choices and outcomes, quality of life, and long-term results. This review provides a detailed overview of epidemiology, pathogenesis, clinical features, and treatment of the disease. However, in this comprehensive review, we have mainly focused on key issues regarding diagnosis/differential diagnosis and clinical management of LV with a holistic approach. In addition, we tried to identify the research gap in the literature to form the basis for further research.

Epidemiology

LV often occurs in young to middle-aged adults and affects woman more often (female:male ratio ~2:3; Criado et al., 2011; Gonzalez-Santiago and Davis, 2012; Micieli and Alavi, 2018; Winkelmann et al., 1974). This increased risk for LV in women might be related to sex-specific physiological conditions, such as pregnancy (Sankar and Hinshaw, 2009) or a higher incidence of LV-associated conditions, such as connective tissue diseases, hypercoagulable states, and venous stasis, in women. The incidence of LV is estimated at 1:100,000 (Alavi et al., 2013; Criado et al., 2011).

Fig. 2. Typical livedo racemosa lesions on the lower legs with vivid, erythematous to purple network-like lines.

Epidemiologic data also suggest that there is a 5-year delay in the adequate diagnosis and management of this condition (Freitas et al., 2018). Possible reasons for the delay in diagnosis can be that patients do not consult dermatologists in the early stages of cutaneous findings, cutaneous lesions usually initially cause minimal subjective complaints, and the current clinical picture can be confused with cutaneous findings that may accompany venous insufficiency, especially venous ulcers.

Pathogenesis

LV pathogenesis is not yet fully known. Initially, it was considered to be vasculitis. However, recent consensus suggests that changes in the local or systemic control mechanism of coagulation lead to the formation of fibrin thrombi in superficial dermal vessels. The thrombotic effect results from defects in the endothelial cell plasminogen activation, platelet dysfunction, or enhanced fibrin formation (Vasudevan et al., 2016). This dermal-vessel thrombosis leads to superficial tissue ischemia and necrosis, causing ulceration and debilitating pain (Amato et al., 2006; Hairston et al., 2006; Vasudevan et al., 2016). Low tissue perfusion further leads to poor wound healing and ineffective killing of microorganisms by leucocytes, enhancing the chance of infection (Vasudevan et al., 2016).

Patients with LV also show decreased flow-mediated vasodilation of the brachial artery, signifying endothelial dysfunction and decreased production or activity of nitrous oxide in endothelial cells, supporting the contribution of endothelial damage to LV (Alavi et al., 2013; Yang et al., 2012). Therapeutic response to immunosuppressive and immunomodulatory agents and association with other autoimmune disorders also supports the involvement of autoimmunity in etiopathogenesis. Increased perfusion pressure

Fig. 3. Hallmark lesion of livedoid vasculopathy, with retiform or stellate purpura distributed to the ankles and painful and small crusted punched-out ulcers located on the perimalleolar area.

Fig. 4. Atrophie blanche with small, residual, round or stellate, porcelain-white atrophic scars surrounded by hyperpigmentation and telangiectasias.

at the ankles also appears to play an important role (Vasudevan et al., 2016). LV can be categorized as primary (idiopathic) or secondary LV, in which a known underlying condition causes the disease (Alavi et al., 2013).

Although some mechanisms in the etiopathogenesis of LV and COVID-19–associated livedoid lesions have similar features, COVID-19 infection-causing LV has not yet been reported (Llamas-Velasco et al., 2020). Recently, COVID-19-induced recurrence of LV in a 34-year-old female patient with no other comorbidities or coagulative disorders has been reported (Valentim et al., 2021).

Histopathology

A clinical presentation of LV is characteristic; however, biopsy is necessary to exclude other entities in the differential diagnosis and confirm LV diagnosis. Characteristic histological findings include thickening (endothelial proliferation) or hyalinized degeneration of the subintimal layer of superficial dermal vessels along with intraluminal fibrin deposits, intraluminal thrombosis, red blood cell extravasation, and scarce perivascular lymphocytic infiltration (Bard

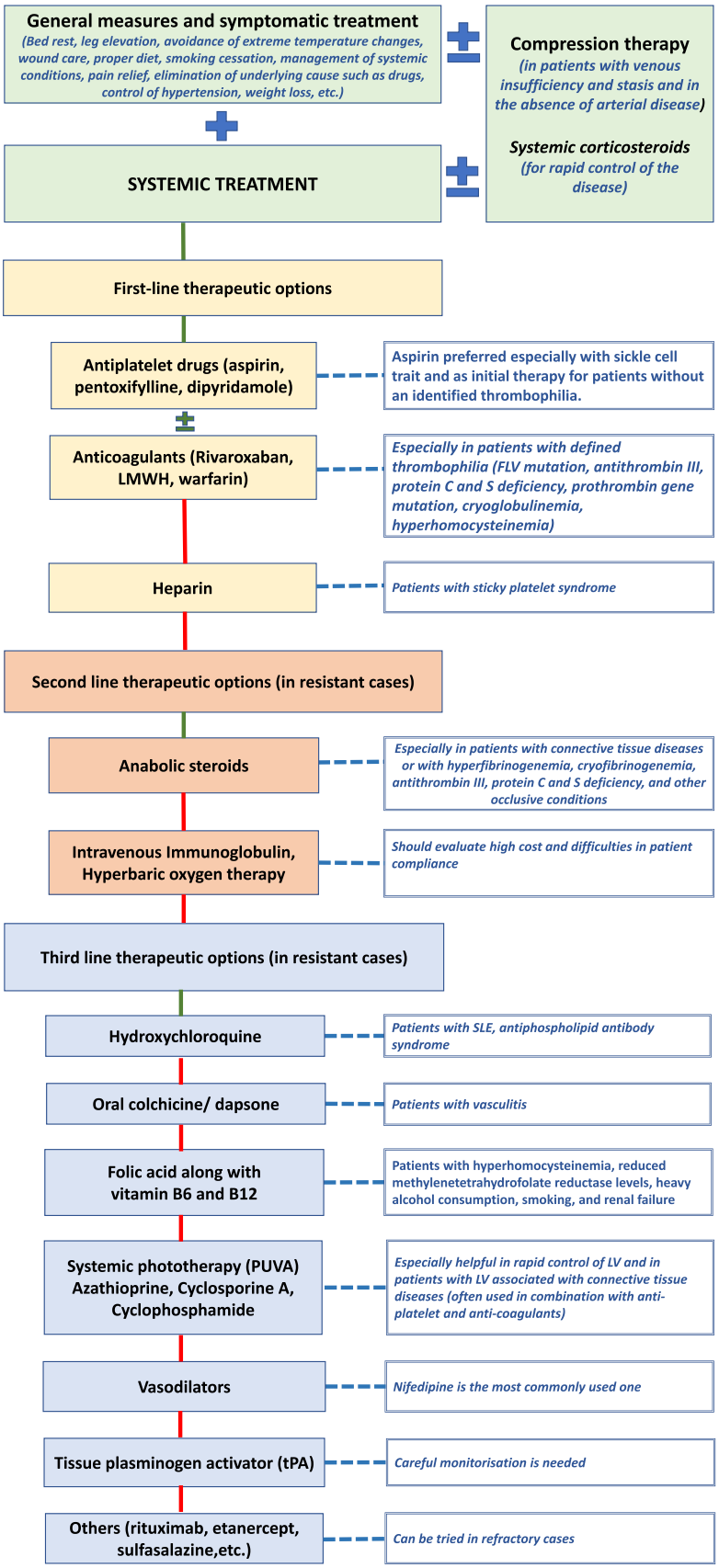

Fig. 5. Algorithmic therapeutic approach of livedoid vasculopathy.

Table 1
Differential diagnosis and their specific characteristic findings

Differential diagnosis	Distinguishing features
Chronic venous insufficiency	Varicose veins, superficial telangiectasias, edema of the lower limbs, stasis dermatitis, ochre dermatitis, abnormal venous Doppler ultrasound findings
Peripheral arterial disease	Pale skin, claudication, painful ulcerations, abnormal arterial Doppler ultrasound findings, abnormal ankle-brachial index test
Cutaneous polyarteritis nodosa	Subcutaneous tender nodules on the legs, ulcerations, digital gangrene, medium vessel involvement, mononeuritis multiplex
IgA vasculitis	Age <10 y, organ involvement (joint, gastrointestinal and renal), IF; IgA
Cutaneous leukocytoclastic angiitis	Clinical and hematoxylin and eosin findings, such as IgA vasculitis; no organ involvement
IgM/IgG vasculitis	Urticaria ± necrotic/ulcerous lesions, IF; IgM/IgG
Cryoglobulinemic vasculitis	Cold exacerbation, Raynaud's phenomenon, acrocyanosis, renal involvement, IF; cryoglobulin II/III
Recurrent macular vasculitis	Recurrent and short-term hemorrhagic macules, hypergammaglobulinemia positive
UV	Urticaria >24 h, postinflammatory pigmentation, ± hypocomplementemia
Normocomplementemic UV	
Hypocomplementemic UV	
Nodular vasculitis	Dark red violet ± ulcerated nodules on the lateral/posterior tibia, lobular panniculitis, hypersensitivity to tuberculosis
Eosinophilic granulomatosis with polyangiitis	ANCA+, eosinophil-rich histopathology, respiratory (rhinitis, asthma history), renal (hematuria), neurological (neuropathy, mononeuritis multiplex), cardiac (eosinophilic cardiomyopathy) and gastrointestinal (polyposis, nausea, vomiting, abdominal pain) involvement
Granulomatosis with polyangiitis	p-ANCA or c-ANCA positive, retiform purpura-like lesions and reticulated ulcerations, pulmonary and renal disease (glomerulonephritis)
Microscopic polyangiitis	p-ANCA positivity, retiform purpura-like lesions and reticulated ulcerations, dermal granuloma, mononeuritis multiplex, pulmonary and renal disease
Sneddon syndrome	Livedo racemosa with cerebrovascular stroke
Others in differential diagnosis of atrophie blanche	Sickle cell disease, hydroxyurea ulcers, malignant atrophic papulosis, polycythemia vera, thalassemia, essential thrombocytosis, chronic myeloid leukemia

ANCA, antineutrophil cytoplasmic antibody; IF, immunofluorescent; Ig, immunoglobulin; UV, urticarial vasculitis

and Winkelmann, 1967; Haunson et al., 2012). No signs of true vasculitis in the form of leukocyte infiltrate on the vessel walls are seen (Criado et al., 2011; Hesse and Kutzner, 2008). Thus, the histopathological findings allow clinicians to better classify LV as vasculopathy instead of immune-complex-mediated necrotizing vasculitis (Fig. 1; Criado et al., 2011; McCalmont et al., 1992).

Histopathological findings depend on the age of the lesion, and due to the focal and segmental involvement pattern of LV, classic histopathological findings may not be observed with the biopsy. Thus, attention should be given to the appropriate biopsy method (Alavi et al., 2013). Early lesions show intraluminal hyaline thrombi in small vessels in the mid- and papillary dermis and fibrinoid materials in the vessel walls and perivascular stroma (Alavi et al., 2013; Georgesen et al., 2020). Fully developed lesions show thickening and hyalinization of vessel walls with endothelial edema and proliferation, along with intraluminal fibrin thrombi, dermal sclerosis, and scarring. Multiple biopsies could be necessary for definitive diagnosis; however, some experts suggest that multiple biopsies could complicate the healing of the ulceration (Fig. 1; Alavi et al., 2013; Criado et al., 2011; Haunson et al., 2012).

Apart from routine histopathology, direct immunofluorescence (DIF) is used. DIF demonstrates immunoglobulin deposition (multiple immunoreactants, especially C3 and immunoglobulin [Ig] M, followed by IgA, and IgG), fibrin, and complement components, although DIF findings are thought to be nonspecific and nondiagnostic (Criado et al., 2011; Khenifer et al., 2009; Nuttawong et al., 2021). In the literature, the incidence of positive DIF in patients with LV ranged from 42.9% to 100% (Criado et al., 2014; Hsiao and Wu, 2010; Nuttawong et al., 2021; Schroeter et al., 1971; 1975). Older patients and more recent lesions (<6 months) had a significantly higher percentage of positive DIF results for LV (Nuttawong et al., 2021).

Genetics

Several hereditary and acquired coagulation abnormalities are involved in LV, including polymorphisms in methylenetetrahydrofolate reductase (MTHFR), plasminogen activator inhibitor-1 (PAI-1), prothrombin, and factor V. The associations between LV and genetic abnormalities show geographical or ethnic differences. a recent systematic review investigating genetic variations identified that PAI-1-675 4G/5G was the most common, accounting for 85.26% of cases (n = 81 of 95), followed by PAI-1 A844G, MTHFR C677T, and MTHFR A1298C variants. Prothrombin G20210A and factor V G1691A were mainly present in patients with LV from Europe, North America, and South America (Gao and Jin, 2021).

Clinical features

Patients with LV often have a history of painful recalcitrant ulcers and whitish scars near the ankles. Burning pain is a pathognomonic prodromal symptom of this entity. Physical examination might reveal lesions in different stages of evolution. The typical clinical appearance of LV consists of three main findings: livedo racemosa, skin ulcerations, and atrophie blanche (Fig. 1; Alavi et al., 2013).

Livedo racemosa is distinguished by vivid, erythematous to purple, network-like lines, mainly due to abnormal perfusion of cutaneous microcirculation (Fig. 2). Naturally, LV is not the only disease in which livedo racemosa can be seen; however, it is generally regarded clinically as an early manifestation of LV. Livedo reticularis and livedo racemosa (broken net pattern) are precursor lesions before ulceration.

Purpuric macules, papules, or retiform or stellate purpura (especially considered as a hallmark lesion) are other important initial findings (Fig. 3). They are often distributed on the ankles, dorsum of the feet, and the lower extremities and usually occur symmetrically. However, some studies also showed lesions on the upper extremities in a small proportion of patients (Lee and Cho, 2020; Rujitharanawong et al., 2021). This is followed by acute-onset, painful, and small crusted ulcers. Ulcers characterize the active stage of the disease. Excruciating pain, causing difficulties in daily life, is a clue for early diagnosis because it precedes ulceration (Vasudevan et al., 2016). Ulcers, characterized by a punched-out appearance on the perimalleolar area, heal within 3 to 4 months with atrophie blanche, small residual round or stellate porcelain-

Table 2
Laboratory testing for livedoid vasculopathy

Hypercoagulable states/ fibrinolytic disorders/ thrombophilia	Factor V Leiden and prothrombin G20210A mutation, protein C, protein S, anti-thrombin-III deficiency, PT/PTTK, aPTT, fibrinogen, D-dimer, lupus anticoagulant, lipoprotein (a), serum homocysteine, MTHFR-C677T polymorphism, prothrombin-G20210A mutation, serum fibrinopeptide A, levels of serum complements (C3, C4), fibrinogen, plasminogen-activator inhibitor activity, antiphospholipid antibodies, cryoglobulin, cold agglutinins and cryofibrinogen, Ig light chain (kappa and lambda) levels, serum folic acid, vitamin B12 and vitamin B6 levels
Connective tissue diseases (systemic lupus erythematosus, antiphospholipid antibody syndrome, rheumatoid arthritis, scleroderma, primary Sjogren's syndrome, polyarteritis nodosa, and undifferentiated connective tissue diseases)	Levels of serum complements (C3, C4), ANCA, ANA, ENA, anti-Ro, anti-La, anti-CCP, rheumatoid factor, cryoglobulin, cryofibrinogen, plasminogen activator inhibitor, anti-beta-2 glycoprotein I, antiphospholipid antibodies (lupus anticoagulant), anticardiolipin antibodies (IgM and/or IgG), and IgM antiphosphatidylserine
Malignancy Hematological (myeloproliferative disorders, paraproteinemia, multiple myeloma) and solid organ malignancies	Ig light chain (kappa and lambda) levels, protein electrophoresis, immunofixation, lipoprotein (a) levels
Infections	Anti-streptolysin-O, throat culture, hepatitis B, hepatitis C, enzyme-linked immunosorbent assay for HIV, COVID-19, swab wound culture, and tissue cultures
Conditions associated with stasis (chronic venous hypertension of the limbs, varicose veins)	Venous Doppler ultrasound, arterial Doppler ultrasound, ankle-brachial/toe-brachial pressure index, venous duplex imaging, plethysmography, and transcutaneous oximetry cardiovascular surgery consultation
Assessing tissue ischemia	Transcutaneous oxygen pressure or partial pressure of oxygen by transcutaneous oximetry adjacent to the ulcer, Doppler flowmetry, laser Doppler perfusion imaging, and microlymphography
Pregnancy	Urine human chorionic gonadotropin
Other	Complete blood count, comprehensive metabolic panel, urinalysis, erythrocyte sedimentation rate, C-reactive protein, peripheral smear, fecal occult blood

ANA, antinuclear antibody; ANCA, antineutrophil cytoplasmic antibody; aPTT, activated partial thromboplastin time; CCP, cyclic citrullinated peptide antibodies; ENA, extractable nuclear antigen antibody; Ig, immunoglobulin; MTHFR, methylenetetrahydrofolate reductase; PT, prothrombin time; PTTK, partial thromboplastin time with kaolin

white atrophic scars surrounded by hyperpigmentation and telangiectasias (Fig. 4; Alavi et al., 2013; Criado et al., 2011; Weishaupt et al., 2019).

Although systemic involvement is not a feature of idiopathic LV, peripheral nervous system involvement (paresthesia or hyperesthesia, mononeuritis multiplex) can be seen due to multifocal thrombosis and ischemia of the vasa nervorum and is the only known extracutaneous manifestation of LV (Criado et al., 2011; Tubone et al., 2013; Vasudevan et al., 2016). A French observational study has revealed a high incidence of peripheral neuropathy (50% of patients), which has been described rarely in the existing literature (Gan et al., 2012; Gardette et al., 2018). Due to the limitations of conventional diagnostic techniques (electromyelography, nerve biopsy), which mainly work with large nerve fibers, a diagnosis of peripheral neuropathy requires special investigations. Gardette et al. (2018) suggested that most patients with LV have neuropathic pain that persists after healing of ulcers despite a normal electromyelography; peripheral neuropathy is probably underestimated. Nerve biopsies also reveals an ischemic process, showing that LV is not only a cutaneous but also a peripheral neurological disease (Gardette et al., 2018). Other systemic and multiorgan involvement might be present in secondary LV associated with autoimmune connective tissue disorders. A dermoscopic examination of LV could show central shallow crusted ulcers, ivory–white atrophic scar-like areas, pigment network or ivory–white structureless areas with a peripheral pigment network, and telangiectatic irregular, linear, and glomerular vessels (Hu et al., 2017; Shen et al., 2019; Wen et al., 2020).

Diagnosis and differential diagnosis

The diagnostic criteria of LV are not well defined, and no treatment guidelines are available (except Delphi-consented expert recommendations; Alavi et al., 2013). A detailed history, dermatological examination, and laboratory work-up are essential for excluding other diseases in the differential diagnosis, demonstrating associated conditions, and, therefore, a diagnosis of LV.

When LV is clinically suspected, a skin biopsy should be taken to confirm the diagnosis. A fusiform incisional biopsy containing subcutaneous fat is the most appropriate biopsy. Alternatively, a 4 to 6 mm punch biopsy may be performed. The best place for a biopsy is the edge of a new ulcer; the biopsy specimen should contain 2 to 3 mm of marginal skin and the eventual ulcer (Alavi et al., 2013).

A differential diagnosis of other common causes of atrophie blanche should be the first step in the clinical work-up. The most common diseases to be considered in the differential diagnosis are lower extremity chronic venous insufficiency, peripheral arterial vascular disease, and vasculitis. Along with clinical signs, abnormal arterial Doppler ultrasound findings and ankle-brachial index test support the diagnosis of peripheral artery diseases. Another main differential diagnosis is cutaneous polyarteritis nodosa, which produces similar cutaneous lesions on the legs. A proper skin biopsy can distinguish LV from vasculitis.

Despite all efforts, no associated factor can be detected in approximately 20% of all cases (idiopathic LV). In the remaining patients, connective tissue disorders, malignancy, hypercoagulable states, and thrombophilia are the most important associated factors (Table 1; Fig. 1; Alavi et al., 2013; Weishaupt et al., 2019).

Laboratory testing

When the diagnosis is confirmed histopathologically, further review of possible underlying diseases should be undertaken. Assessment, of course, should begin with a complete history, review of systems, and physical examination to assess findings suggestive of underlying diseases. Laboratory tests for thrombophilia are recommended in all patients (Ishibashi et al., 2009; Sankar and Hinshaw, 2009; Winkelmann et al., 1974). Further examination, such as coagulating factors and their mutations, are required for hereditary or acquired thrombophilia.

Detailed laboratory research for connective tissue disorders, such as systemic lupus erythematosus, antiphospholipid antibody syndrome, rheumatoid arthritis, scleroderma, and mixed connective tissue disease, should be performed in the presence of relevant findings suggestive of these diseases. In addition, Ig kappa and lambda chain levels, protein electrophoresis, and immunofixation should be performed when paraproteinemia or solid organ cancers are suspected. Again, in the presence of an underlying in-

Table 3
Therapeutic options of livedoid vasculopathy

Treatment (reference)	Mechanism of action	Dose	Side effects
Antiplatelets			
Aspirin (acetylsalicylic acid) (Acland et al., 1999; Castillo-Martínez et al., 2014; Criado et al., 2013; Drucker and Duncan, 1982; Gan et al., 2012; El Khoury et al., 2012; Krueger et al., 2020; Lee et al., 2003; Okada et al., 2008)	Cyclooxygenase inhibitor; suppresses thromboxane A2 and prostaglandin I2; promotes vasodilation; prevents platelet aggregation and thrombus formation; improves ulcer healing	75–325 mg, higher doses (up to 325 mg, 3 × 1 daily) offering better results	Angioedema, urticaria, gastrointestinal bleeding, Reye's syndrome, salicylism (central nervous system, tinnitus)
Pentoxifylline (Criado et al., 2021; Feng et al., 2014; Gan et al., 2012; Krueger et al., 2020; Lee et al., 2003; Marzano et al., 2003; Meiss et al., 2006; Sams, 1988; Song et al., 2020; Yong et al., 2012)	Competitive nonselective phosphodiesterase inhibitor; reduces inflammation; decreases blood viscosity; modifies red blood cell structure to reduce exocytosis; increases the inflow circulation; reduces platelet aggregation and thrombus formation	400 mg every 3 × 1 daily	Dyspepsia, nausea, vomiting, abnormal liver function, alopecia
Dipyridamole (Agirbasli et al., 2011; Drucker and Duncan, 1982; Krueger et al., 2020)	Phosphodiesterase inhibitor; inhibits the synthesis of thromboxane A2; stimulates release of prostaglandin I2; inhibits both adenosine deaminase and phosphodiesterase, preventing the degradation of cAMP (inhibitor of platelet function and aggregation)	Initial: Dose of 50 mg, twice daily (up to75 mg 4 × 1)	Bleeding, dizziness
Clopidogrel (Kunzler and Chong, 2018)	Antiplatelet agent; inhibits prostaglandin synthesis; irreversibly binds to P2Y12 ADP receptors on platelets and prevents platelet aggregation	75 mg once daily	Hemorrhage, vomiting, pancytopenia, thrombotic thrombocytopenic purpura, hypersensitivity reactions
Ticlopidine (Hegemann et al., 2002; Okada et al., 2008)	Prodrug that is metabolized to an active form; blocks ADP receptor that is involved in GP IIb/IIIa receptor activation leading to platelet aggregation	250 mg twice daily	Aplastic anemia, thrombotic thrombocytopenia purpura, black-box warning of neutropenia, bleeding, hepatic impairment
Buflomedil hydrochloride (Criado et al., 2011)	Antiplatelet effect; nonspecific calcium channel antagonist and alpha-blocker; increases inflow circulation	Oral 150 mg, 3–4 × daily or 300 mg twice daily	Flushing, headache, vertigo, dizziness, gastrointestinal discomfort
Beraprost sodium (Tsutsui et al., 1996)	Analog of PGI2; stable, orally active prostacyclin analog with vasodilatory, antiplatelet and cytoprotective effects	120 μg/day initially and at a dose of 60 μg/d subsequently	Headache, flushing, diarrhea, leg pain, and nausea
Abciximab (Vasudevan et al., 2016)	Monoclonal antiglycoprotein IIb/IIIa receptor antibody for glycoprotein IIb/IIIa receptor of human platelets; inhibits platelet aggregation by preventing binding of fibrinogen, von Willebrand factor, and other adhesive molecules	0.25 mg/kg IV bolus followed by continuous IV infusion of 0.125 μg/kg/min for 12 hr	Bleeding, thrombocytopenia
Sarpogrelate hydrochloride (Osada et al., 2010; Vasudevan et al., 2016)	Antagonist of 5-hydroxytryptamine 2A receptor (serotonin); antiplatelet and vasodilator effects	Orally 300 mg/day	Hemorrhage, thrombocytopenia, agranulocytosis, jaundice
Anticoagulant			
Warfarin (Browning and Callen, 2006; Di Giacomo et al., 2010; Kavala et al., 2008; Nakamura et al., 2011; Nakayama et al., 2017; Noda et al., 2011; Osada et al, 2010; Saoji and Madke, 2017; Vieira et al., 2016; Yoshioka et al., 2018)	Vitamin K antagonist; inhibits vitamin-K dependent synthesis of biologically active forms of various clotting factors in addition to several regulatory factors; increases fibrinolytic activity	Oral/IV; 2–5 mg once daily for 1–2 days, then adjust dose based on international normalized ratio (maintained between 2 and 3) Maintenance: 2–10 mg oral/IV once daily	Teratogen, bleeding, jaundice, necrosis, purple toe syndrome, osteoporosis, valve and artery calcification, and drug interactions
Heparin (Abou Rahal et al., 2012; Di Giacomo et al., 2010; Francès and Barete, 2004)	Decreases blood viscosity; increases fibrinolytic activity; increases activity of tissue plasminogen activator	Dose of 5000 U/12 hr, subcutaneously	Bleeding, thrombocytopenia
LMWH (enoxaparin, dalteparin, nadroparin) (Abou Rahal et al., 2012; Cardoso et al., 2007; Di Giacomo et al., 2010; Francès and Barete, 2004; Goerge et al., 2010; Hairston et al., 2003)	Decreases blood viscosity; increases fibrinolytic activity	Enoxaparin 40 mg/day or 100 IU/g per injection bidaily, dalteparin sodium 5000 IU/day, subcutaneously	Late hypersensitivity, injection site reactions, increase in liver enzymes
Rivaroxaban (Chen et al., 2017; Drabik et al., 2014; Drerup and Goerge, 2017; Evans et al., 2015; Franco Marques and Criado, 2018; Jiménez-Gallo et al., 2018; Kerk et al., 2013; Lee and Cho, 2020; Lee and Kim, 2016; Leisenring et al., 2020; Miguel et al., 2020; Weishaupt et al., 2016; 2019; Winchester et al., 2015)	Direct inhibitor of factor Xa; new LMWH; decreases blood viscosity; increases fibrinolytic activity	10 mg bidaily, orally	Hypermenorrhea, nose bleeding, bleeding tendency during dental procedures, and hemarthrosis
Other vitamin K antagonists (preprohormone, acenocoumarin, fluindione) (Francès and Barete, 2004)	Decreases blood viscosity; increases fibrinolytic activity	Require monitoring international normalized ratio (maintained between 2–3)	Bleeding tendency
Sulodexide (Song et al., 2020)	Highly purified mixture of glycosaminoglycans, including dermatan sulfate and LMWH	Oral 250 lipasemic units 3 × 1 daily	Transient gastrointestinal intolerance, nausea, dyspepsia
Fibrinolytics			
Recombinant tissue plasminogen activator (Agirbasli et al., 2011; Antunes et al., 2010; Deng et al., 2006; Johnson et al., 1995; Klein and Pittelkow, 1992; Murrell et al., 1995)	Fibrinolysis of microvascular thrombi; restores the circulation; promotes wound healing	10 mg IV every 4 hr/day, 14 day	Bleeding, allergic reactions

(*continued on next page*)

Table 3 (*continued*)

Treatment (reference)	Mechanism of action	Dose	Side effects
Antiplatelets			
Danazol/stanozolol (Acland et al., 1999; Criado et al., 2015; Feng et al., 2014; Hsiao and Chiu, 1996; 1997; Rizzo et al., 1986; Wakelin et al., 1998)	Synthetic steroids and pituitary gonadotropin inhibitors; have fibrinolytic activity	Danazol: 200 mg/day or 4 mg/kg/day) for a short duration of 4–12 week Stanozolol: 4 mg/day	Hirsutism, acne, steroid-like side effects, alopecia, menstrual disturbances, clitoral hypertrophy
Vasodilators			
Nifedipine (Purcell and Hayes, 1986; Vasudevan et al., 2016)	Dihydropyridine calcium channel blocker; reduces vasospasm; decreases peripheral arterial vascular resistance; increases supply of oxygen	10–20 mg 3 × 1 per day	Hypotension, sinus node dysfunction, atrioventricular node dysfunction, reflex tachycardia
Cilostazol (Mendiratta et al., 2016)	Quinolinone derivative; phosphodiesterase III inhibitor; antiplatelet agent and vasodilator	100 mg twice daily	Headache, diarrhea, tachycardia, hypotension, cardiac arrhythmias
Nicotinic acid (Winkelman, 1974)	Niacin is a B3 vitamin; decreases levels of very low-density lipoproteins and low-density lipoproteins, while increasing levels of high-density lipoproteins	1–3 × daily	Severe prolonged hypotension
Alprostadil-alpha (Prostaglandin E1) (Kawakami et al., 2007; Mofarrah et al., 2013)	Direct effect on vascular smooth muscle; causes vasodilation	60 μg/day over 3 hr for 5 days, followed by a monthly infusion of 60 μg over 3 hr	Apnea, bradycardia, pyrexia, hypotension
İloprost (Magy et al., 2002)	Synthetic analog of prostacyclin PGI2; inhibits ADP, thrombin, and collagen-induced aggregation of platelets	IV via infusion pump at a rate of 0.5 ng/kg/min for 6–8 h/day (maximum tolerated dose of 2 ng/kg/min)	Hypotension, headache, nausea, vomiting, and diarrhea
Ketanserin (Rustin et al., 1989)	S2 serotonergic receptor blocker; prevents vasoconstrictive effect of serotonin; increases cutaneous blood flow	Dose of 20 mg 3 × daily	Drowsiness, fatigue, headache, sleep disturbances
Anti-inflammatory			
Colchicine (Gan et al., 2012; Lee et al., 2003; Vasudevan et al., 2016)	Alkaloid; inhibition of inflammation caused by tubulin disruption; anti-inflammatory effects with neutrophil inhibition	Oral 0.5 mg, 2 × 3 × daily	Gastrointestinal disturbance, including abdominal pain, nausea, vomiting, diarrhea
Dapsone (Acland et al., 1999; Gan et al., 2012; Irani-Hakime et al., 2008; Micielli and Alavi, 2018; Winkelman, 1972)	Sulfone drug; anti-inflammatory effects with neutrophil inhibition; immunosuppressive and antibacterial properties	Oral doses of 50–100 mg/day	Nasal congestion, syncope, anemia, hallucinations
Sulfasalazine (Bisalbutra and Kullavanijaya, 1993; Micielli and Alavi, 2018)	Sulphapyridine metabolite; anti-inflammatory and/or immunomodulatory properties; inhibition of platelet aggregation by 5-aminosalicylic acid prevents cytokine release from mononuclear cells	500 mg, 3 × 1 daily, orally	Headache, facial edema, paresthesia of the lips, nausea, rash, itchiness, metallic taste
Doxycycline (Keller et al., 2008)	Second-generation tetracycline antibiotic; anti-inflammatory and antimicrobial, bacteriostatic effects by inhibition of protein synthesis	Dose of 100 mg twice daily	Tooth enamel hypoplasia, yellow–gray discoloration of teeth, gastrointestinal irritation, esophagitis
Hydroxychloroquine (Gan et al., 2012; Irani-Hakime et al., 2008; Keller et al., 2008; Vasudevan et al., 2016)	Aminoquinoline; affects function of lysosomes in humans; inhibits antigen presentation of the cell; reduces inflammatory response	Up to 0.6 mg/kg/day	Headache, drowsiness, visual disturbances, convulsions, rhythm, conduction disorders including QT prolongation, torsades de pointes, ventricular tachycardia, ventricular fibrillation
Immunosuppressants			
Prednisolone (Alavi et al., 2013; Criado et al., 2011; Gan et al., 2012; Marzano et al., 2003; Micieli et al., 2018)	Anti-inflammatory action; antifibrinolytic effect; immunosuppressive effect	0.5–1 mg/kg/day (prednisolone or equivalent)	Steroid side effects
Azathioprine (Alavi et al., 2013; Criado et al., 2011; Gan et al., 2012; Micieli et al., 2018)	Prodrug of 6-mercaptopurine; inhibits purine synthesis along with inhibition of B and T cells	2–3 mg/kg/day	Bone marrow hypoplasia, hepatotoxicity, infection
Cyclophosphamide (Alavi et al., 2013; Criado et al., 2011; Gan et al., 2012; Micieli et al., 2018)	Alkylating agent; cytotoxic effect due to cross-linking of strands of DNA and RNA; inhibition of protein synthesis; immunosuppressive effect	1.5–2.5 mg/kg/day	Neutropenia, alopecia, nausea, vomiting, diarrhea, sterility, birth defects, mutations, cancer
Cyclosporine (Alavi et al., 2013; Criado et al., 2011; Micieli et al., 2018)	Calcineurin inhibitor; potent immunomodulatory agent; suppresses lymphocyte activity; inhibits expression of tissue factor of monocytes, which is a vital component in triggering the coagulation cascade	3–5 mg/kg/day	Hypertrichosis, gingival hyperplasia, nephrotoxicity, hypertension
Supplements			
Folic acid (Anderson et al., 2013; Errichetti and Stinco, 2016; Meiss et al., 2006)	Required for homocysteine remethylation; necessary to maintain adequate plasma homocysteine and serum folate levels	5 mg/day	Abdominal cramps, diarrhea, sleep disorders, irritability, confusion, stomach upset
Vitamin B12/B6 (Anderson et al., 2013; Errichetti and Stinco, 2016; Meiss et al., 2006)	Additional supplementation along with folic acid	Vitamin B6 (1500 μg/day) and vitamin B12	Nausea, stomach upset, diarrhea, drowsiness, flushing, numbness/tingling
Miscellaneous			

(*continued on next page*)

Table 3 (*continued*)

Treatment (reference) Antiplatelets	Mechanism of action	Dose	Side effects
Intravenous immunoglobulin (Amital et al., 2000; Bounfour et al., 2013; Kim et al., 2015; Kofler et al., 2021; Kreuter et al., 2004; Monshi et al., 2014; Oravec et al., 1995; Ozden et al., 2020; Pitarch et al., 2005; Ravat et al., 2002; Tuchinda et al., 2011)	Acts by inhibiting Fc receptor function in macrophages, T cells, and B cells, leading to decreased cytokine production; reduces immune complex deposition in small vessels; inhibits thromboxane synthetase; decreases vasoconstriction	Monthly infusions in the dose of 0.4–2 g/kg over 2–3 consecutive days	Allergic reactions, headache, flushing, chills, myalgia, wheezing, tachycardia, hypotension
Hyperbaric oxygen (Banham, 2013; Bhutani et al., 2012; Bollmann et al., 2011; Fernandes, 2009; Juan et al., 2006; Ray et al., 2015; Verma, 2013; Yang et al., 2003)	Enhances tissue oxygenation and microvascular perfusion by stimulating nitric oxide synthesis; accelerates angiogenesis and fibrinolysis; accelerates fibroblast proliferation; diminishes tissue reperfusion injury; increases growth of granulation tissue; bacteriostatic and bactericidal effects	Pure oxygen or 100% 1.5–2 hr, 1–3 × daily	Lung damage, changes in vision, oxygen poisoning
Psoralen plus ultraviolet A (Choi and Hann, 1999; Lee et al., 2001; Tuchinda et al., 2005)	Decreases ability of lymphocytes to respond to cytokine production; induces release of immunosuppressive factors	2–3 × per week	Sunburn-like reaction, phototoxic erythema, skin ageing and skin cancer
Rituximab (Zeni et al., 2008)	Monoclonal anti-CD20 antibody	1.0 g, two infusions, 14 days apart	Neonatal harm, infection risk, severe immunosuppression
Antitumor necrosis factor (etanercept) (Gao and Jin, 2020)	Anti-inflammatory properties; act mainly by close interaction between various inflammatory cytokines and coagulation	25–50 mg once a week for 12 consecutive weeks	Infection risk, immunosuppression

ADP, adenosine diphosphate; cAMP; IV, intervenous; LMWH, low molecular weight heparin; PGI2, prostaglandin I2

fection suspicion, tests for hepatitis and HIV infection should be performed (Table 2).

Treatment

Treatment of LV is very challenging for physicians. Because the incidence of LV is relatively low, there are no large series of studies on its treatment. Therefore, the level of evidence is not high, and treatment recommendations are generally based on case series, small clinical trials, or expert recommendations. No single therapeutic approach is effective for all patients. Furthermore, there are no predictive clinical or biologic indicators for the severity or frequency of LV flares. For this reason, many options are often used in combination. Moreover, there is no fixed endpoint for treatment in patients who respond to treatment. Once the ulcer has healed, treatment may be discontinued; however, long-term treatment may be necessary to maintain healing. Treatment selection can be based on cost, adherence, patient comorbidities, and clinical experience. The main treatment options are presented in Table 3. Our approach is reviewed herein, and the therapeutic algorithmic approach is presented in Figure 5.

Although the best approach to treatment is unclear, general measures (e.g., wound care, smoking cessation, compression, and pain management) are important components of LV therapy along with pharmacological treatment. Wound care should include maintaining a moist wound environment and controlling superinfection. Patients should be encouraged to stop smoking because of the negative effects of smoking on wound healing. Compression therapy is also helpful in patients with venous insufficiency. Improvement may be due to the stimulating effect of compression on fibrinolytic activity and controlling edema. Pain secondary to livedoid vasculopathy can be severe. Nonsteroidal anti-inflammatory drugs, such as indomethacin or acetaminophen, can be used. Tricyclic antidepressants, gabapentin, pregabalin, or carbamazepine may be preferred for neuropathic pain and are valuable for patients with persistent painful ulcerations (Alavi et al., 2013; Micieli and Alavi, 2018).

The first-line therapeutic step is antiplatelet therapy (aspirin, dipyridamole, and pentoxifylline). Aspirin (300 mg once daily) is preferred, especially as the initial therapy for patients without an identified thrombophilia and/or with sickle cell trait. Tolerability, wide availability, and low cost are important advantages of this compound. Dipyridamole and pentoxifylline (600 mg twice daily) can be favored in combination with aspirin in unresponsive cases or alone in patients who cannot tolerate aspirin. In patients with identified thrombophilia and/or without significant improvement after antiplatelet treatment, anticoagulants can be used. Low molecular weight heparin (1 mg/kg/d) or rivaroxaban (2 × 15 mg in the first week, then continue with 20 mg once daily) are typically used at our center. Anticoagulants were the most reported monotherapy in a recent systematic review by Micieli and Alavi (2018). Rivaroxaban is often the treatment of choice in recent years due to the advantage of oral administration and the unnecessity of international normalized ratio follow-up, which increases patient compliance.

Anabolic steroids (prednisolone and equivalents, danazol 4 mg/kg/d) were the second most used and effective treatment in clinical trials. They inhibit coagulation while increasing fibrinolysis. They can be the next step, especially in patients with connective tissue diseases, hyperfibrinogenemia, and other occlusive conditions. Systemic steroids can also be added to the main treatment to achieve rapid disease control at any timepoint.

In resistant cases, preference for therapeutic choices is based on availability, clinical experience, and patient-related factors (comorbidities, age, sex, compliance). Intravenous Ig, hyperbaric oxygen treatment (1.5-2-hour sessions, three times daily for 3-4 weeks) and fibrinolytics (recombinant tissue plasminogen activator, 10 mg/d for 14 days) have also been reported to be effective alternatives. These treatments would be more suitable for refractory LV due to high cost and difficulties in patient compliance. All other therapeutic options are summarized in Table 3. Hydroxychloroquine in patients with systemic lupus erythematosus and antiphospholipid antibody syndrome, and colchicine in patients with vasculitis can be reasonable options in combination with antiplatelet and/or anticoagulant therapies. Vasodilators (used as maximum tolerated dose), anti-inflammatory agents, immunosuppressives, and psoralen-ultraviolet A could be used as third-line options. Vitamin supplements, especially folic acid and vitamin B12/B6, are required for homocysteine remethylation; thus, they can be added to treatment. All these agents are used often in combination with antiplatelets and anticoagulants (Alavi et al., 2013; Micieli and Alavi, 2018).

Conclusion

LV is associated with a variety of underlying conditions, and no single etiology has been identified. Since the therapeutic approach should be modified according to etiopathogenetic mechanisms, possible systemic associations should be investigated. Several therapeutic options with different success rates are being used. However, randomized controlled trials with a high evidence level should be performed to determine the best therapeutic approach in the treatment of LV. Furthermore, a multidisciplinary approach is necessary for effective and proper treatment.

Conflicts of interest

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N/A

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