Livedoid Vasculopathy: An Integrative Review of Etiology, Pathogenesis, Histopathology, Diagnosis and Therapeutic Strategies.

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Abstract—**Livedoid vasculopathy (LV) is a rare, chronic vascular disorder characterized by painful ulcerations, livedo racemosa, and the formation of atrophie blanche, predominantly affecting the lower extremities. Once considered an inflammatory vasculitis, LV is now recognized as a thrombo-occlusive disease primarily involving the dermal microcirculation with minimal inflammatory involvement. The pathogenesis of LV is multifactorial, involving hypercoagulability, endothelial dysfunction, and impaired fibrinolysis, often associated with inherited or acquired thrombophilia conditions. Histopathological findings typically reveal fibrin thrombi within small dermal vessels, endothelial proliferation, and limited perivascular inflammation, distinguishing it from true vasculitis disorders.**

Clinically, LV presents with recurrent, painful ulcers that heal slowly and leave characteristic porcelain-white scars, significantly impacting patient quality of life. Diagnosis remains challenging due to overlap with other vascular and dermatological conditions, requiring a combination of clinical evaluation, histopathology, and laboratory investigations to identify underlying prothrombotic states. Current therapeutic strategies focus on improving blood flow and preventing thrombosis using anticoagulants, antiplatelet agents, and supportive measures, while advanced therapies such as intravenous immunoglobulin and targeted biologics show promise in refractory cases.

This review provides a comprehensive overview of the etiology, pathogenesis, clinical manifestations, histopathology, diagnostic challenges, and evolving therapeutic approaches of LV, highlighting the need for standardized treatment protocols and further research into its underlying mechanisms.

Index Terms—**Livedoid vasculopathy; thrombo-occlusive disorder; dermal microcirculation; hypercoagulability; atrophie blanche; fibrin thrombi; endothelial dysfunction; diagnosis; anticoagulant therapy; chronic ulcers**

I. INTRODUCTION

Livedoid vasculopathy (LV) is an uncommon, chronic, and painful thrombosis of the dermal microcirculation which typically affects the lower limbs. LV is typified by livedo racemosa, painful recurrent ulcers and porcelain-white stellate scars known as atrophie blanche [1-3]. LV was earlier believed to be a form of inflammatory vasculitis; however, it is now apparent that it is a thrombo-occlusive vasculopathy with minimal or absent inflammation and is therefore not like primary vasculitides [4,5]. The illness is predominant to women aged 15 to 50. It normally appears on both ankles, tops of feet or lower legs [6-8].

LV may be caused by a host of factors which include endothelium issues, excess clotting and fibrin degradation issues. Hereditary thrombophilia's such as the absence of protein C and S, factor V Leoden mutation and antithrombin III deficiency, and acquired diseases such as antiphospholipid syndrome, and high levels of [9-13] plasminogen activator inhibitor-1 have also been known to predispose to thrombotic events. TNF-a and other inflammatory mediators have also been implicated in the vascular damage and clotting of blood particularly in situations that are not responsive to the treatment [14-16]. With this additional information, still one-third of the cases remain idiopathic, meaning that other, yet unidentified mechanisms are also operating [17,18].

It is characterized by small fibrin thrombi in the dermal vessels, foci of hyalinization, endothelial proliferation and only a minor portion of perivascular inflammation [19]. Such characteristics distinguish it amongst leukocytoclastic vasculitis and other skin diseases that result in ulcers. The presence of similarities in diagnosis with venous insufficiency,

vasculitis, or neuropathic ulcers is common in that they all take longer to diagnose. This may result in wrong diagnosis and prolonged sickness [20-22]. The most common current treatments are anticoagulants, antiplatelet, vasodilators, and immunomodulators, whose responses are variable and, no guidelines about the standard treatment options exist. The recent methods such as targeted therapies such as direct oral anticoagulants and TNF-a inhibitors such as adalimumab have been promising in the treatment of hard to manage cases. This demonstrates the change of LV management [23-25].

II. ETIOLOGY

Increasingly, livedoid vasculopathy (LV) is perceived by people as a thrombo-occlusive disorder rather than inflammatory vasculitis. Microvascular thrombosis of dermal circulation is the primary cause of LV. Its primary cause is hypercoagulability which may be precipitated by inherited and acquired thrombophilic disorders. Protein C, protein S, and antithrombin III problems and mutations in the gene of factor V Leiden and prothrombin, and antiphospholipid antibodies are known. All these predispose the blood clots to develop in the small blood vessels of the skin [1,4].

The malfunction of the fibrinolytic system is also a massive component of the issue, as well as coagulation issues. An increased concentration of plasminogen activator inhibitor-1 (PAI-1) particularly those with 4G/4G polymorphism have been associated with reduced degradation of fibrin, which maintains thrombus in affected vessels [5,6]. Additionally, LV has been also associated with autoimmune connective tissue disorders such as systemic lupus erythematosus and antiphospholipid syndrome indicating the possibility of an immune system component to it in a few cases [7,18]. Vascular injury and thrombosis are likely to be exacerbated by individuals at risk by trauma or cold [8,9].

This trend indicates that LV is not a result of a single factor, but rather by a multitude of diverse prothrombotic and endothelial consequences all resulting in vascular impediment. Idiopathic cases are those which do not have any underlying condition after a lot of testing [10,19]. Overall, a complex vascular pathology in combination of thrombosis, disrupted fibrinolysis, and potentially immunologic factors is the cause of LV.

III. PATHWAY OF COAGULANT AND GENETICS

Numerous inherited thrombophilic defects and deficiencies disrupt the balance between the procoagulant and anticoagulant processes, making LV hypercoagulable.

1.Antithrombin III, Protein C and Protein S deficiency.

Deficiencies, be it inherited or acquired, cause unchecked production of thrombin in the dermal microvasculature [1-4,11-15].

2.Factor V (F5 gene) mutation at Leiden.

The G1691A mutation confers the production of Factor V which is resistant to inactivation by activated protein C (APC resistance). This enhances the thrombin production, which predisposes thrombosis.

3.The Prothrombin Gene (F2, G20210A) is mutated.

Due to this mutation, there is an increase in the level of prothrombin (Factor II) which improves the conversion to thrombin and leads to the formation of fibrin clots.

4.Gene Variants for MTHFR

Variants like C677T (frequently not reported but involved in some cases of LV) can result in hyperhomocysteinemia, which progresses through endothelial damage and promoting thrombosis.

5.PAI-1 (or) 4G/4G Polymorphism of 4G/4G Plasminogen Activator Inhibitor-1.

Be stimulation of PAI-1 by the 4G allele inhibits fibrinolysis and stabilizes the thrombi in dermal vessels [5,6].

6.Dysregulation of Fibrinolytic System.

Besides coagulation, the destruction of vascular occlusion is also enhanced by the inability to break the clots. The low concentration of plasmin deposition is caused by the low concentration of PAI-1 leading to a continuous deposit of fibrin. There are those that inhibit fibrinolysis because their tissue plasminogen activator (tPA) functions are diminished.

7.Autoimmune and Immunogenetic Associations

Some LV patients are associated with autoimmune connective tissue disorders:

The antiphospholipid antibodies are linked to the antiphospholipid syndrome (APS) and systemic lupus erythematosus (SLE) that additionally contribute to thrombosis developing through platelet and endothelial cell activation [7,18]. This indicates an immunogenetic response whereby, autoantibodies trigger coagulation activation as well as endothelial destruction.

8.Genetically predisposed Environmental Factors in people.

Exposure to cold causes vasospasm and endothelial dysfunction. Thrombosis in the case of local trauma affecting skin microvesses the causes of thrombosis are stimulated by local trauma, which worsens the disease in genetically predisposed patients [8,9].

9.Idiopathic Situations

Even after a comprehensive workup, some LV patients do not contain any thrombophilic mutation or systemic disease. They can be either involving undetectable genetic variants or mild endothelial dysfunction, but it falls in the category of idiopathic LV [10,19].

IV. PATHOGENESIS:

The LV pathophysiology is not completely understood. The two are a primary form or idiopathic form and a secondary form. Its pathogenesis is mainly intraluminal fibrin thrombi that clog the postcapillary venules that causes tissue death, prolonged ischemia and eventually atrophie blanche typical to it [1,2].

Several prothrombotic tissues have been linked to the emergence of LV. Some of these are inherited protein C and S deficiencies, antithrombin III deficiency, factor V Leiden mutation, prothrombin G20210A mutation, antiphospholipid antibodies and others [4-6]. The alteration in fibrinolysis has been linked to longer duration of vascular blockage and tissues that have undergone thrombus resolution which includes increased levels of plasminogen activator inhibitor-1 (PAI-1) and 4G/4G gene polymorphism of PAI-1 [7, 8].

Ischemia causes painful scars and ulcers which are slow to heal. This pathophysiological point of view places the importance of fibrinolytic dysfunction and coagulation in LV.

In contrast to inflammatory vasculitis, livedoid vasculopathy (LV) is mostly a thrombotic tissue of the small blood vessels of the skin. The blockage of mini dermal vessels by fibrin thrombi causes ischemia, infarction, tissue ulceration and this is the main method of spreading the disease [11,12].

Hypercoagulability is one of the significant factors of disease process. It is often linked with such problems as the increased amounts of plasminogen activator inhibitor-1, factor V Leiden mutation, deficiency of antithrombin III, and the deficiency of protein C and S [13,14]. The endothelial injury slowed blood flow, and the accumulation of fibrin around the blood vessels prolong healing and increase the impairment of perfusion [15,16]. Histological alterations of LV include intraluminal thrombosis, segmental hyalinization, and endothelial cell proliferation in the absence of a large amount of leukocytolytic infiltration [17]. In recent studies, prothrombotic conditions might not have autoimmune processes as their main cause, including the presence of antiphospholipid antibodies, and lupus anticoagulant [18,19]. These are the factors that have contrary effects to maintain the chronic ulceration and microvascular occlusion in the left ventricle [20].

V. CLINICAL FEATURES

The disease follows unique phases in a classic clinical process. Early symptoms are erythematous to violaceous painful and persistent papules or macules, particularly on the ankles and the back of the feet [1]. The lesions may turn into painful, slow healing, shallow, punched out ulcers [2].

Atrophie blanche or stellate, porcelain-white scars with the telangiectasias surrounding the areas of previous erosion are typical clinical characteristics of LV [3]. Atrophie blanche can be differentiated against other ulcerative dermatoses to this scarring pattern. Although there may be no open ulcers, the pain is often reported as intense, burning even in the absence of open ulcers [4]. Livedo racemosa, an irregular net-like violaceous appearance may develop as an independent or a pre-ulcerative effect of the disease [5]. Whereas there have been cases of involvement of upper limbs and trunk, the lesions are usually bilateral and most commonly on the lower third of the legs [6].

The disease follows a pattern of periods of exacerbation and remission. Necrotic zones can become bigger, slowing down healing, increasing the chance of infection and enduring debilitation [7]. Due

to ischemic damage of the vasa nervorum, occasionally, patients can also have peripheral neuropathic disorders such as paresthesia or hyperesthesia [8].

Diagnosis is often late due to clinical manifestation similarities with other conditions involving vascular or dermatological alterations, including venous stasis ulcers or vasculitis.

1. First Lesions: Patterns of Purpura and Livedo

Livedo racemosa is a net-like, violaceous discolouration of the skin that can be present in association with the small, reddish-purple spots or petechiae, commonly the first indication of LV. These changes are normally the most visible ones and usually appear at the lower legs, feet or ankles [13].

2.Development of Ulcers

The initial purpuric lesions usually result in painful shallow lesions as the disease advances. These ulcers may be of different sizes, repetitive and most often have irregular borders. In most cases, they appear above pressure points such as the lateral and medial malleoli [16].

3.Blanche Atrophie: Post Healing Scarring

Healed ulcers usually leave behind atrophic scars atrophic in nature, termed as atrophie blanche or white, star-shaped, atrophic scars. These glossy smooth spots that are often surrounded by telangiectasia and pigmentation are radiance signs of prior ischemic damage [11]. As an example, case photographs of long-standing LV cases showed porcelain scars surrounded by brown discoloration [13].

4.Sensory Symptoms and Chronic Pain.

Pain is one of the primary symptoms of LV that can be disproportionate to the ulcer size. Many of these patients complain of burning, stinging, or numbness that can be triggered by severe nerve damage or by small-vessel ischemia [14], [16].

5.Course Recurrent/Chronic.

LV is chronic and is in most cases periodic. The ulcers can also be repeated at the same sites over the months or years and often healed slowly and with scars [15].

VI. HISTOPATHOLOGY

LV is seen as fibrin thrombi in the lumen of superficial dermal vessels and the vessels being less than 40 umdiameter particularly capillaries and postcapillary venules with little smooth muscle and no internal elastic lamina is seen on microscopic examination [1]. To distinguish LV and real inflammatory vasculitis's, such changes occur in the presence of minimal to no perivascular inflammatory infiltration [3]. Leukocytoclastic, another typical manifestation of vasculitis is normally absent and, in some cases, inflammatory cells such as neutrophils are either absent or scant, in the affected vessels resulting in ulceration and ischemia of the respective tissue [5].In more chronic stages, the affected vessels are hyalinized and thickened with an eventual plugging of the vessels by organized thrombus, leading to ulceration and ischemia of the affected tissue [5]. Dermal sclerosis and epidermal atrophy in the tissue around these vessels are responsible in the development of the characteristic porcelain-white scars referred to as atrophie blanche [6].

Unlike granular deposition pattern that is seen in immune complex mediated vasculitis, the deposits are typically diffuse and uniform [8].

A deep punch or excisional biopsy (4-6 mm) is the most suitable method of histopathologic diagnosis to provide a representative sample of the affected vasculature. This biopsy must preferably be sampled on the margin of an active ulcer, including the adjacent normal skin [1]. The clinical appearance of LV is so distinctive that the biopsy procedure may not be necessary, and may cause ulceration or hard healing [9]. Because of (i)The absence of nuclear fragmentation and polymorphonuclear neutrophils surrounding the dermal vessels, which occur earlier than the presence of the lesions in LV, allow us to better define it as occlusive vasculopathy. (ii) Vascular wall leukocyte penetration deficiency. (iii) Hyalinization and deposition of fibre in the vascular wall. (iv) Most of the patients present with normal serum complement levels, and there is no visible circulation of immune complex in the body. [14].

Features of Histopathology:

Cases of dermal vessel occlusion caused by thrombus are common in skin biopsies. Deposition of fibrin, swelling of endothelium, and segmental hyalinization

of small vessels, as well as low perivascular inflammation, are typical findings [17]. As an example, direct immunofluorescence has shown the deposition of immune complexes (IgG, IgM, C3, fibrin) in vessel walls, in addition to increased levels of hematoxylin and eosin staining proving the thrombotic and immune-mediated nature of the disease [17].

VII. DIAGNOSIS

Livedoid Vasculopathy (LV) remains a difficult clinically diagnosed disease because of its similarity with other vasculitis and thrombotic diseases. A conclusive diagnosis must be closely made by combining histopathology, physical findings, clinical history, and exclusion of a differential diagnosis.

The patients that are suspected to have LV are clinically those with chronic, painful ulcerations in the lower extremities, especially around the ankles, livedo racemosa, and residual atrophie blanche. These are patients mostly women aged between third and fifth decades. These symptoms are usually bilateral and may become more severe during hot weather or when the patient is standing for a long time.

A biopsy must focus on the edge of a new lesion to identify any active vascular changes. Even though this is not pathogenic; direct immunofluorescence can reveal non-specific deposition of IgM, IgA, C3 and fibrin on vessel walls.

After clinical pathologic diagnosis, laboratory screening of thrombophilia conditions is necessary. Prothrombotic factors, including factor V Leiden mutation, high lipoprotein(a), hyperhomocysteinemia, or antiphospholipid antibodies, are present in up to 66% of LV cases although not all of them are found to show coagulation abnormalities [4][8]. Such studies guide treatment decisions and help in distinguishing between idiopathic and secondary variants.

VIII. DIFFERENTIAL DIAGNOSIS:

LV should be distinguished against a few vascular and inflammatory disorders that resemble its cutaneous manifestations because of its complicated manifestation. The most important of them are cutaneous polyarteritis nodosa (cPAN), antiphospholipid syndrome (APS), Sneddon syndrome, cryoglobulinemia, and chronic venous insufficiency.

In contrast to the thrombotic microangiopathy found in LV, the histological features of cutaneous PAN demonstrate a real necrotizing medium-size vessel vasculitis even though it is often presented in the form of nodules, ulcers, and livedo racemosa. On the same note, Sneddon syndrome and APS are also likely to be related to neurological results and systemic thrombotic events, respectively, yet may also be characterized by livedo patterns and ulceration [4].

Atrophies blanche and ulcers can be found in chronic venous insufficiency, but these are usually accompanied by systemic symptoms: purpura, arthralgia, or renal involvement; therefore, a completely different location of atrophy blanche is seen, along with varicosities and venous reflux on Doppler [7][8].

Lastly, LV could be differentiated by these mimics due to the presence of dermal vessel occlusion and fibrin deposition, the absence of notable perivascular inflammation and a favorable thrombophilia profile. A multidisciplinary pathology, hematology, and dermatology approach often must be used to provide accurate classification and management [4][7].

IX. TREATMENT APPROACHES:

The livedoid vasculopathy (LV) treatment strategy targets the thrombo-occlusive pathology as opposed to inflammation. The goals include restoring skin perfusion, preventing ulcers, and managing pain.

1. Antiphospholipid and anticoagulant.

Direct oral anticoagulants (DOACs) e.g. warfarin or rivaroxaban or low molecular weight heparin (LMWH) are widely used and are the first line of treatment especially in patients with known thrombophilia [9][10]. Thrombosis of dermal vessels is prevented with the help of these medications. Aspirin or pentoxifylline can sometimes be combined with it to achieve hemorheological or antiplatelet effects [11].

2.Intravenous immunoglobulin (IVIG)

IVIG has shown significant results of healing ulcers and analgesic effects to patients that are non-responsive to anticoagulation, or who have autoimmune characteristics [10][12]. Its immunomodulatory effect is especially useful when there is suspected immune dysregulation.

3.Ablative Endovenous Therapy.
Incompetent veins in some patients, particularly those with venous insufficiency, endogenous laser ablation or sclerotherapy may lead to long term ulcer healing and symptom management [13]. These therapies decrease the pressure-induced dermal ischemia and enhance the venous flow.

4.Compression therapy.
Compression garments are also beneficial as an adjuvant treatment, especially in the management of patients with chronic venous insufficiency because they enhance venous circulation and edema reduction and healing of ulcers [13].

5.Thrombolytic and Fibrinolytic Processes.
Polymorphisms or excessive levels of plasminogen activator inhibitor-1 (PAI-1) may impair fibrinolysis in LV. Targeted agents that inhibit fibrinolytic processes, or tissue plasminogen activator (tPA), have been shown to be effective in such cases, particularly in those individuals who are genetically prone to it [12] [18].

6.Supplemental Treatments
Other methods consist of: Anabolic steroids (e.g., danazol) in thrombophilia cases [9]. Connective tissue disease patients [10] [12] Immunosuppressants.
pain relief, neuropathic or analgesic, as required [14].

7.Sequential and Systematic Management:
Recent reviews propose an algorithmic treatment approach:
I. Begin with anticoagulant/antiplatelet medication.
II. Immunomodulatory drugs should be used on non-responders.
III. Add IVIG or fibrinolytics in situations where the treatment is not successful.
IV. Alter as per the coagulation profiles and comorbidities of the patient [2] [5].

Prospects and Challenges of Livedoid Vasculopathy (LV) in the future:
1.Chronicity and Relapse:
LV typically has a remitting-relapsing course which is aggravated in warmer seasons, possibly due to vasodilation or increased outside temperature. Long-term care complexity is enhanced by the fact that most of the patients suffer from several years of painful ulcers which recur and several lesions occur simultaneously at different stages of healing.

2. Difficulties:
LV may result in both cutaneous and systemic complications:
I. Complications of the skin:
Atrophie blanche Atrophic scars on the kidney, which are permanently pigmented, ivory-white, and stellate in shape, and are due to non-healing ulcers. Since ulcerated skin is a point of entry of microbes, secondary infections are common. Fibrosclerosis or skin stiffness due to recurrent scarring may inhibit mobility.

II. Neurological involvement:
In LV, ischemic vasa nervosa thrombotic events result in peripheral neuropathy, including mononeuritis multiplex, in up to 38% of patients. This aggravates the quality of life through pain, paresthesia, and weakness of muscle.

3. Delayed Diagnosis and Disability.
There is a major issue of the overlap of features with other ulcerative skin conditions that leads to the problem of the average delay in diagnosing LV (3.4 to 5 years). This delay has the consequences of an increased risk of chronic pain syndromes and disfigurement; increased pain and psychological distress; and a prolonged deterioration in functional ability and quality of life.

4. Permanent Disability Risk
Without treatment, LV may turn chronic and result in pain which may cause:
I. Problems with general activities.
II. Decreased ability to work
III. Psychosocial consequences due to chronic symptoms and noticeable skin damage.

5. Depending on the case, prognosis is different, Anticoagulants (like rivaroxaban) or immunoglobulin therapy can get some patients into remission in cases of refractory cases. However, 20-40 percent of the patients may fail to respond to traditional therapy especially when the underlying thrombophilia condition is unknown or untreated.

X. CONCLUSION

Livedoid vasculopathy is a disease that affects the blood vessels in the skin for a long time. It causes ulcers, livedo racemosa and atrophie blanche. Doctors have found out that livedoid vasculopathy is mainly caused by the blood clotting much the body having trouble breaking down clots and the blood vessels not working properly. This is different from what they thought before which was that it was caused by inflammation. Livedoid vasculopathy can be caused by problems people are born with or things that happen later in life. Sometimes the cause is still not known. To figure out if someone has livedoid vasculopathy doctors need to look at the skin under a microscope and do tests to see if the blood is clotting much. The main treatment for livedoid vasculopathy is to stop the blood from clotting much and to help the symptoms. There are treatments being developed but they do not work the same for everyone and it is still hard to diagnose livedoid vasculopathy. We need to learn more, about what causes livedoid vasculopathy and find a way to treat it so that people can have better lives and feel better for a long time. Livedoid vasculopathy is a disease and more research is needed to help people with livedoid vasculopathy.

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