



Minireview

Submitted: 7.11.2012
 Accepted: 30.1.2013
 Conflict of interest
 None.

DOI: 10.1111/ddg.12064

Livedoid vasculopathy – current aspects of diagnosis and treatment of cutaneous infarction

Nina Kerk, Tobias Goerge

Department of Dermatology, University Hospital Münster, Germany

Summary

Livedoid vasculopathy is a rare, chronic, recurrent disease of the cutaneous microcirculation. Its typical clinical manifestation is a triad which consists of livedo racemosa of the skin, episodic painful ulcerations of the distal aspects of the legs and a healing process leaving small porcelain-white scars called atrophie blanche. As an important result of recent research, livedoid vasculopathy has been defined as a coagulation disorder classified as a vasculopathy different from inflammatory vasculitis. This differentiation adds to the current pathophysiologic understanding and supports the therapeutic rationale with respect to the use of new systemic anticoagulants. The prevention of irreversible residual scarring and the improvement of patients' quality of life are the main goals in treating cutaneous infarction and require early and consequent treatment. This article presents current knowledge on diagnosing this rare disease and offers practical guidance on its therapy.

Introduction

Livedoid vasculopathy was first reported in the 1950s by Feldaker as a coagulation disorder and termed livedo reticularis with summer ulcerations [1]. The later-employed term segmental hyalinizing vasculitis addresses histologic features of the disease, but wrongly emphasizes the inflammatory aspect [2]. The English-language acronym PPURPLE (painful purpuric ulcers with reticular pattern of lower extremities) makes dramatic the involvement of the legs. The misleading term “livedo vasculitis” is also often employed, even though on closer examination the clinical features of livedoid vasculopathy are being described.

The incidence of livedoid vasculopathy is estimated at 1: 100,000 with a distinct female preference (female/male ratio 3: 1) [3]. The mean age of onset is 45 years. Commonly the disease occurs in late adolescence up to the age of 30 years [4]. The path from the first symptom to the correct diagnosis is often long and difficult for the patient. Being alert to this rare but easily treatable disease makes an early diagnosis possible, from which particularly young patients profit [5].

Clinical manifestations

Livedoid vasculopathy is a chronic disease with a dynamic and episodic course. The full-blown form of the disease is characterized by the triad livedo racemosa, ulcerations on the distal aspects of the legs and atrophie blanche (Figures 1, 2). These typical features do not necessarily have to be present simultaneously. Livedo racemosa presents with lacy livid-red streaks on the skin that result from disturbed perfusion of the cutaneous microcirculation and can be viewed as a precursor stage to ulceration. In the acute stage of livedoid vasculopathy, ulcerations develop with necrotic areas as the result of cutaneous ischemia with consecutive inadequate blood supply to the overlying skin layers. Atrophie blanche is a porcelain-white scar that represents the remnants of the cutaneous infarction at the end of the restructuring process and is irreversible. Accompanying postinflammatory hyperpigmentation can in the further course of time be partially resorbed. Atrophie blanche is also termed capillaritis alba [6] and is not specific for livedoid vasculopathy, but also occurs, for example, in chronic venous insufficiency.



Figure 1 Complete clinical picture of livedoid vasculopathy after recurrent disease occurrence characterized by the triad: livedo racemosa, crusted ulcerations and atrophie blanche as well as postinflammatory hyperpigmentation. It took about 10 years from first symptoms to diagnosis. During treatment with systemic anticoagulation, no further cutaneous infarctions occurred.



Figure 2 Close-up view of the malleolar region of a patient with typical porcelain-white radial atrophie blanche scarring as a remnant of painful cutaneous infarctions. Perilesional livedo racemosa is also seen.

The disease is almost exclusively located on the leg and there particularly in the region of the ankle with extensions to the back of the foot and the distal lower leg. General symptoms such as fatigue or malaise are not reported by the patients. Angiologic-phlebologic tests to exclude the most important differential diagnostic considerations for leg ulcers are usually normal. A diagnostic signpost is the localized sensation of burning pain at the ankle that is reported by the patients in the prodromal phase before the appearance of ulceration. This sensation of pain is of great importance, as in this phase the full-blown form of ischemic cutaneous infarction with consecutive scarring can still be prevented.

Livedoid vasculopathy is a purely cutaneous form of ischemia. Thus, no systemic involvement is to be expected and no further organ diagnostics is required. On the other hand, livedoid vasculopathy-like lesions can be found in autoimmune disorders such as e.g. scleroderma or systemic lupus erythematosus as well as in tumors. However, these changes develop as a secondary phenomenon [7, 8].

Histology

Histologically, characteristically capillary vessels in the upper and middle dermis are occluded by fibrin thrombi as well as fibrinoid degeneration of the vessel walls in the sense of a vasculopathy. In contrast to primary vasculitis, only a slight or no perivascular inflammatory infiltrate is found initially and later the secondary inflammation is less prominent. In an advanced stage a secondary inflammatory infiltration. In the event of vessel destruction, extravascular erythrocytes are also observed as a result of micro-hemorrhages. Hyalinization of the dermis and capillary walls characterizes atrophie blanche.

Differential diagnostic considerations

An exact history with the typical episodic disease course and the pain symptoms as well as a biopsy of a skin lesion in the acute stage leads to the diagnosis of livedoid vasculopathy. Additional laboratory tests to determine associated risk factors and to exclude other possibilities, especially vasculitis, may be performed. In particular, the differentiation from polyarteritis nodosa can be difficult clinically. In the prototypical case, the latter disease features palpable subcutaneous painful nodules that eventually ulcerate. Histologically, in polyarteritis nodosa particularly vascular occlusion in the deeper dermis as well as distinct signs of vascular inflammation with perivascular extravasation of granulocytes is seen. Therapy success with corticosteroids indicates polyarteritis nodosa and largely excludes livedoid vasculopathy. Conversely, clinical improvement during systemic anticoagulation more likely speaks for livedoid vasculopathy.

Pathogenesis

Today livedoid vasculopathy is characterized as an occlusive disorder of the capillary microcirculation leading to cutaneous ischemia and infarction [9–11]. Often abnormal coagulation parameters and further livedoid vasculopathy-associated factors can be detected, resulting in continuous thrombosis of the microcirculation (Table 1). Livedoid vasculopathy usually manifests on the lower leg, so that rheologic conditions there, such as increased perfusion pressure and the Virchow triad, also seem to play an important role in its development. As the youngest member of the livedoid vasculopathy-associated

Table 1 Prothrombotic markers associated with livedoid vasculopathy.

Laboratory parameter	Genetic test
▶ Cryoglobulin	▶ Factor-V-G1691A mutation
▶ Cryofibrinogen	▶ Prothrombin-G20210A mutation
▶ Homocysteine	▶ MTHFR-C677T polymorphism
▶ Vitamin B6	▶ MTHFR-C677T polymorphism (methylenetetrahydrofolate reductase)
▶ Vitamin B12	▶ PAI-1-4G/5G polymorphism (plasminogen activator inhibitor)
▶ Folic acid	
▶ Protein C	
▶ Protein S	
▶ Anti-thrombin-III deficiency	
▶ Antinuclear antibodies	
▶ Lupus anticoagulants	
▶ Anticardiolipin antibodies	
▶ β2-Glycoprotein-1 antibodies	
▶ Lipoprotein(a)	

parameters, lipoprotein (a) has been described as a risk factor [4, 12]. Patient registries are necessary in order to identify further associated risk factors in the collective.

Therapy

Due to the lack of multicenter studies in face of the low incidence of the disease, livedoid vasculopathy represents a great therapeutic challenge to the treating physician – treatment to date has always been an individual treatment attempt with off-label use. Therapy is urgently indicated to prevent pain and the progressive scarring in the malleolar region. In view of the basic coagulation disorder, systemic anticoagulation appears sensible. The greatest treatment experience in German-speaking Europe exists for the use of low molecular weight heparin. In a daily dosage of 1 mg/kg s.c. (for enoxaparin) satisfactory results can be achieved for the majority of patients – with a favorable side effect profile and rapid response [5, 13, 14]. In phases of more frequent ischemic attacks, an increase of dose into the therapeutic range of 1 mg/kg in the morning and the evening may be indicated. In routine practice the patients should be advised to keep a pain journal. When the value of the visual analog scale (VAS) rises, anticoagulation is required; in quiet phases, therapy may also be interrupted temporarily.

The multiple points of attack of the heparins on thrombin synthesis justify their use in livedoid vasculopathy of varying causes. According to the literature therapy with phenprocoumon is also available as an option [15], while here the necessity for monitoring of therapy (INR 2–3) and the sole

effect on vitamin K-dependent factors must be remembered. Administration of folic acid is indicated if methylenetetrahydrofolate reductase levels are abnormal [16]; in addition, systemic anticoagulation may also be required. The use of fibrinolytic agents should be based on strict indications and reserved for specialized centers due to the risk of massive hemorrhages [17]. Experimental data prove the benefits of immunoglobulins in livedoid vasculopathy [18, 19], but anticoagulation is considerably less expensive.

Accompanying measures such as compression stockings, avoidance of massive temperature changes as well as topical application of perfusion-promoting formulations may also be helpful.

The newest data with respect to systemic anticoagulation demonstrate that the oral factor-X inhibitor rivaroxaban can successfully prevent cutaneous ulcerations in livedoid vasculopathy [20]. Rivaroxaban represents an injection-free alternative to low molecular weight heparins and improves the quality of life according to patient opinion. A controlled clinical study on therapeutic response to rivaroxaban is expected.

Conclusions

Even though the exact pathogenetic molecular mechanisms of the abnormal coagulation in the cutaneous microcirculation is still a subject of research, the classification of the disease as “vasculopathy” helps to differentiate it from the vasculitides. Correspondingly, early systemic anticoagulant therapy, which can positively impact the disease, is justified. Unfortunately, due to the rarity of the disease, the treating physician is forced to provide off-label therapy. The development of a patient registry and the necessary licensing studies are important steps for improving the current situation – both for the physician and also for the patient.

Correspondence to



Priv.-Doz. Dr. Tobias Goerge
Department of Dermatology, University Hospital Münster

Von-Esmarch-Straße 58
48149 Münster, Germany

E-mail: tobias.goerge@ukmuenster.de

References

- 1 Feldaker M, Hines EA, Jr., Kierland RR. Livedo reticularis with summer ulcerations. *AMA Arch Derm* 1955; 72: 31–42.
- 2 Bard JW, Winkelmann RK. Livedo vasculitis. Segmental hyalinizing vasculitis of the dermis. *Arch Dermatol* 1967; 96: 489–99.
- 3 Fritsch P, Zelger B. [Livedo vasculitis]. *Hautarzt* 1995; 46: 215–24; quiz 22-3.
- 4 Goerge T, Weishaupt C, Metze D, Nowak-Gottl U, Sunderkotter C, Steinhoff M, Schneider SW. Livedoid vasculopathy in a pediatric patient with elevated lipoprotein(a) levels: prompt response to continuous low-molecular-weight heparin. *Arch Dermatol* 2010; 146: 927–8.
- 5 Goerge T. Niedermolekulare Heparin-Therapie zur Behandlung der Livedovaskulopathie. *Aktuelle Dermatologie* 2010; 36: 484–87.
- 6 Metz J, Sturm G. [Atrophie blanche (so-called capillaritis alba)]. *Hautarzt* 1974; 25: 105–9.
- 7 Marzano AV, Vezzoli P, Berti E. Skin involvement in cutaneous and systemic vasculitis. *Autoimmun Rev* 2012 Aug 16. [Epub ahead of print].
- 8 Gonzalez-Santiago TM, Davis MD. Update of management of connective tissue diseases: livedoid vasculopathy. *Dermatol Ther* 25: 183–94.
- 9 Callen JP. Livedoid vasculopathy: what it is and how the patient should be evaluated and treated. [comment]. *Arch Dermatol* 2006; 142: 1481–2.
- 10 Jorizzo JL. Livedoid vasculopathy: what is it? *Arch Dermatol* 1998; 134: 491–3.
- 11 Papi M, Didona B, De Pita O, Frezzolini A, Di Giulio S, De Matteis W, Del Principe D, Cavalieri R. Livedo vasculopathy vs small vessel cutaneous vasculitis: cytokine and platelet P-selectin studies. *Arch Dermatol* 1998; 134: 447–52.
- 12 Emerging Risk Factors C, Erqou S, Kaptoge S, Perry PL, Di Angelantonio E, Thompson A, White IR, Marcovina SM, Collins R, Thompson SG, Danesh J. Lipoprotein(a) concentration and the risk of coronary heart disease, stroke, and non-vascular mortality. *JAMA* 2009; 302: 412–23.
- 13 Hairston BR, Davis MD, Gibson LE, Drage LA. Treatment of livedoid vasculopathy with low-molecular-weight heparin: report of 2 cases. *Arch Dermatol.* 2003; 139: 987–90.
- 14 Sunderkotter C, de Groot K. Therapie von Vaskulitiden und Vaskulopathien. *Hautarzt* 2008; 59: 382–93.
- 15 Browning CE, Callen JP. Warfarin therapy for livedoid vasculopathy associated with cryofibrinogenemia and hyperhomocysteinemia. *Arch Dermatol* 2006; 142: 75–8.
- 16 Meiss F, Marsch WC, Fischer M. Livedoid vasculopathy. The role of hyperhomocysteinemia and its simple therapeutic consequences. *Eur J Dermatol* 2006; 16: 159–62.
- 17 Deng A, Gocke CD, Hess J, Heyman M, Paltiel M, Gaspari A. Livedoid vasculopathy associated with plasminogen activator inhibitor-1 promoter homozygosity (4G/4G) treated successfully with tissue plasminogen activator. *Arch Dermatol* 2006; 142: 1466–9.
- 18 Amital H, Levy Y, Shoenfeld Y. Use of intravenous immunoglobulin in livedo vasculitis. *Clin Exp Rheumatol* 2000; 18: 404–6.
- 19 Kreuter A, Gambichler T, Breuckmann F, Bechara FG, Rotterdam S, Stucker M, Altmeyer P. Pulsed intravenous immunoglobulin therapy in livedoid vasculitis: an open trial evaluating 9 consecutive patients. *J Am Acad Dermatol* 2004; 51: 574–9.
- 20 Kerk N, Drabik A, Luger T, Schneider SW, Goerge T. Rivaroxaban prevents painful cutaneous infarctions in Livedoid Vasculopathy. *Br J Dermatol* 2012 Oct 27. [Epub ahead of print].