Case report

Livedoid vasculopathy

Vasculopatia livedoide

José Roberto Provenza\textsuperscript{a}, Lucas Eduardo Pedri\textsuperscript{a,\textast}, Gabriel Mesquita Provenza\textsuperscript{b}

\textsuperscript{a} Pontifícia Universidade Católica de Campinas, Hospital e Maternidade Celso Pierro, Serviço de Reumatologia, Campinas, SP, Brazil
\textsuperscript{b} Pontifícia Universidade Católica de Campinas, Hospital e Maternidade Celso Pierro, Serviço de Radiologia, Campinas, SP, Brazil

ARTICLE INFO

Article history:
Received 18 September 2014
Accepted 25 September 2015
Available online 19 March 2016

Introduction

Livedoid vasculopathy (LV) is a recurrent, chronic and painful skin disease, characterized by lesions that arise as punctate or lenticular purple-colored macules and/or papules occurring in the lower limbs (lower third of the legs and ankles), which commonly progress to ulceration, and subsequently heal slowly over weeks or months, giving rise to pearly atrophic scars (white atrophy), punctate telangiectasia, and brownish pigmentation, accompanied by a racemous livedo.\textsuperscript{1-3}

The disease usually settles bilaterally in the legs, often causing edema in the lower third of the limbs. Livedoid vasculopathy mainly affects women (about three women for every man) between 15 and 50 (mean 32) years old.\textsuperscript{2,3}

We report a case of a female patient with livedoid vasculopathy, with excellent healing of lower limb ulcers after using an anti-TNF agent.

Case report

Female patient, 60, married, tradeswoman. Twelve years ago, this patient began a clinical picture of bilateral ulcers in her legs and feet, accompanied by color changes, with intense worsening in cold weather. Initially, the superficial ulcers were few in number, with a gradual increase in their number and depth. The patient had no other systemic and/or joint complaint, no comorbidities, and no family history of rheumatic disease.

On physical examination, no change in cardiac, pulmonary and musculoskeletal systems was noted. The lower limbs (legs and feet) presented with an intense livedo racemosa (Fig. 1), with multiple infected, deep ulcers showing destruction of subcutaneous fat and allowing muscle visualization (Fig. 1).

In 2010, the patient had already been treated with several doses of corticosteroids (20–60 mg/day), with only
slight improvement and always with recurrent lesions after decreasing the dose. She had also been treated with a combination of aspirin 200 mg/day and pentoxifylline 800 mg/day, with no clinical improvement. In 2011, the patient was treated with methotrexate 15 mg/week in association with corticosteroids, but to no avail.

Her lab work showed no change in blood count, renal function, liver function and urinary sediment. The complement proteins (C3 and C4) were normal; ANA 1/320 with a fine speckled pattern. Anti-DNA, anti-RNP, anti-Sm, anti-RO, antidiiodiprotein antibodies (IgM and IgG), lupus anticoagulant, rheumatoid factor, and cryoglobulins were negative; ESR: 25 mm, and CRP: 2.4 mg/dL. An ulcer biopsy was obtained, and the pathological examination described occlusion of dermal blood vessels, caused by deposition of intravascular fibrin; and thrombosis associated with segmental hyalinization and endothelial proliferation, with the presence of a discrete perivascular inflammatory infiltrate, suggestive of livedoid vasculopathy/Milian’s white atrophy.

In 2012, after the failure of multiple treatments, a combination of the anti-TNF agent adalimumab and corticosteroids was instituted, with a subsequent decrease of corticosteroids. A year after this therapeutic regimen, the patient showed a significant improvement of her lower limb ulcers (Fig. 2).

**Discussion**

Livedoid vasculopathy is a disease whose pathophysiology is not well understood. This fact reflects the many synonyms for this disease, such as Milian’s white atrophy, livedoid vasculitis, segmental hyalinizing vasculitis, livedoid vasculitis, livedo reticularis with summer ulcers, and PURPLE (Purpuric painful ulcers with Reticular Pattern of the Lower Extremities).1

This vasculopathy may be primary or secondary. In the first type, this condition is not associated with any other disease. On the other hand, the secondary form is commonly related to thrombophilia (factor V Leiden mutation, protein C and/or S deficiency, hyperhomocysteinemia, prothrombin gene mutation), and to connective tissue diseases (SLE, cryoglobulinemia, APS). Therefore, in the face of a suspicion of this diagnosis, it is important to start a clinical investigation of the patient and his/her family, with particular emphasis on hypercoagulable states and inflammatory diseases.1,4 We suggested the exclusion of all those conditions that may determine punch-like (“piecemeal”) reticulated ulcerations and difficult-to-heal conditions; such disorders can cause stellate-like whitish scars (i.e., septic and leukocytoclastic vasculitides).2

In addition to a complete physical examination, the doctor should request a complete blood count, coagulation tests, CRP levels, fibrinogen, anti-nuclear factor, anti-DNA antibody, rheumatoid factor, antiphospholipid antibodies, and cryoglobulins. In addition, it is important to get a Doppler ultrasound of lower limbs, with the aim of discarding chronic venous stasis.4 With the exception of fibrinogen dosage, the patient in this study obtained results for all tests suggested.

Originally, this entity was considered as a true vasculitis, wherein the ischemic-thrombotic changes were due to a primary inflammatory process. However, many authors no longer accept this concept. Currently, one believes that the primary pathophysiological mechanism is a vaso-occlusive process resulting from thrombosis of small- and medium-caliber dermal vessels, considering that inflammatory changes are found
primarily in late lesions, consisting of a secondary event. The thrombosis into these vessels would occur through multiple changes in the coagulation cascade – from platelet dysfunction to a defect in the production of tissue plasminogen activator.\(^1\)\(^2\)

Furthermore, the link between coagulation and inflammation has been investigated in cases of LV, taking into account that thrombin activates those receptors activated by protease type 1 (which, in inflammatory cells, produce inflammatory mediators such as IL-6, IL-8, chemotactic substances of monocytes, and adhesion molecules) and, moreover, recruits leukocytes toward the intravascular environment.\(^1\)

As noted in this patient’s biopsy, in the histological description of livedoid vasculopathy one can observe occlusion of vessels of the dermis through deposition of intravascular fibrin and by intraluminal thrombus, besides segmental hyalinization and endothelial proliferation. The perivascular mixed inflammatory (neutrophilic at its onset, and then lymphocytic) infiltrate arises at a minimum degree. In general, direct immunofluorescence shows deposition of immunoglobulins, fibrin, and components of complement.\(^1\)\(^4\)

Largely due to its uncertain pathogenesis, there is no a single effective treatment for this skin condition. Current treatment options are based on reports of isolated cases, or of case series. Most treatments aim to improve the physical manifestations and alleviate the pain.\(^5\)

The therapeutic arsenal – described in the literature – consists of antiplatelet and anticoagulant agents, fibrinolytic agents, vasodilators, phototherapy with PUVA, hyperbaric chamber, and immunosuppressants (corticosteroids, cyclosporine, sulfasalazine, immunoglobulin). All these agents are described in the literature, in attempts of ulcer treatment.\(^5\)

Among antiplatelet drugs and hemorrhagic agents, acetylsalicylic acid and pentoxifylline, respectively, have been successfully used in the treatment of LV, and their association is one of the most commonly used therapeutic regimens.\(^5\)

Yang et al. reported that 13 of 27 patients with LV responded to a combination of local care of wounds, rest, and low-dose aspirin in combination with dipiridamol.\(^6\) A case report described the successful treatment of LV associated with sickle cell trait with ASA.\(^7\) Sams et al. reported the use of pentoxifylline in eight patients; in seven, a significant improvement of ulcerations was noted.\(^8\) Our patient did not benefit from the combination of these two drugs.

Immunosuppressive agents are generally used for recurrent cases, such as rescue therapy.\(^9\) However, the use of methotrexate was not effective for our patient.

Sheinberg et al. described a case of a 38-year old female with LV refractory to treatment with anticoagulants and immunosuppressants, and who obtained a good response after the institution of rituximab. These authors reported that, in spite of its unknown etiology, LV correlates strongly with immune complex diseases; and its histology shows consistently inflammatory infiltrates; it may come that B lymphocytes are involved in the pathogenesis of this disease, but further studies are needed to clarify this point.\(^10\) In this report, we have succeeded in healing our patient’s ulcers after the use of adalimumab. To our knowledge, this is the first report describing the treatment of LV with an anti-TNF agent.

Tumor necrosis factor (TNF) contributes to the development of thrombosis, because TNF stimulates the expression of tissue factor by endothelial cells (i.e. an activator of the extrinsic coagulation pathway) and of thrombomodulin (a potent inhibitor of coagulation).\(^11\) Thus, adalimumab, which is a fully human anti-tumor necrosis factor monoclonal antibody, can reduce the formation of thrombi into dermal vessels, actively participating in the pathophysiology of livedoid vasculopathy and providing a new perspective to its treatment.

Conflicts of interest

The authors declare no conflicts of interest.

REFERENCES