Pharmacology and therapeutics

Livedoid vasculopathy and hypercoagulability in a patient with primary Sjögren’s syndrome

Raquel Cardoso, MD, Margarida Gonçalo, MD, Oscar Tellechea, MD, PhD, Rosa Maia, MD, Catarina Borges, MD, J. A. Pereira Silva, MD, PhD, and Américo Figueiredo, MD, PhD

Abstract

Background  A 31-year-old woman presented with a 5-year history of painful ulcerations, palpable purpura, porcelain-white atrophic scars of the malleolar region and dorsal aspect of the feet, livedo reticularis on the limbs, arthralgia, xerophthalmia, and xerostomia.

Methods  Skin biopsy revealed vessel wall hyalinization and thrombosis of the microvasculature with a very scarce dermal inflammatory infiltrate. Biopsy of the oral mucosa showed mononuclear infiltration of an intralobular duct of a salivary gland.

Results  Laboratory studies, including autoantibodies and inflammation markers, were normal, except for a positive rheumatoid factor. Coagulation screening revealed C677T methylenetetrahydrofolate reductase (MTHFR) mutation, with a normal serum homocysteine. The patient was treated with oral methylprednisolone (32 mg/day with progressive reduction) and enoxaparin (20 mg/day subcutaneously), with complete ulcer healing within 4 months.

Conclusion  Livedoid vasculitis or vasculopathy has not been referred to previously in association with Sjögren’s syndrome, but may be associated with other autoimmune disorders and anomalies of coagulation, namely factor V Leiden mutation, protein C deficiency, and MTHFR mutation, associated or not with hyperhomocysteinemia, a condition that seems to confer an increased risk of recurrent arterial and venous thrombosis. We stress the importance of anticoagulant therapy for ulcer healing and for the prevention of other thrombotic events.

Introduction

Livedoid vasculitis (LV), also known as livedoid vasculopathy or livedo with summer/winter ulcerations, was first described by Bard and Winkelmann in 1967 as a chronic vaso-occlusive disorder of small dermal vessels affecting mainly young and middle-aged women. It is characterized by livedo reticularis with recurrent and painful ulcerations of the lower limbs, with winter or summer exacerbations, that progress to porcelain-white, stellate, atrophic scars surrounded by hyperpigmentation and telangiectasia, often referred to as “atrophie blanche of Millian”. Histopathology reveals the typical pattern of segmental hyalinization, endothelial swelling, and thrombotic occlusion of dermal arterioles, surrounded by a scarce perivascular lymphocytic infiltrate, without leukocytoclasis.

LV may be associated with autoimmune diseases, such as antiphospholipid syndrome, lupus erythematosus, or scleroderma, which may have associated coagulation disorders, or with thrombogenic disorders, such as factor V Leiden mutation, protein C deficiency, Sneddon’s syndrome, and methylenetetrahydrofolate reductase (MTHFR) mutation, associated or not with hyperhomocysteinemia.

We describe a patient with primary Sjögren’s syndrome (SS) and LV with persistent ulcers on the lower limbs associated with a hypercoagulability state: homozygosity for the C677T MTHFR mutation.

Case Report

A 31-year-old woman was referred to the Department of Dermatology with a 5-year history of persistent, very painful, bilateral, symmetric ulcers of the lower limbs resistant to multiple therapies [hyperbaric oxygen, antiplatelet drugs, pentoxifylline, intravenous immunoglobulin (IVIG)]. During the last year, the patient had also complained of Raynaud’s phenomenon, progressive xerostomia, and xerophthalmia. For the last 3 months, she reported both inflammatory arthralgia, affecting mainly the feet and ankles with morning stiffness lasting around 30 min, and mechanical arthralgia affecting the hands. She had undergone an uncomplicated pregnancy 5 years previously and had used oral contraceptives for 2 years. Her personal and family medical histories were irrelevant.

On the lower limbs, mainly on the malleolar region and dorsal aspect of the feet, there were several deep ulcers,
between 0.5 and 2 cm in diameter, with a purpuric and necrotic border, surrounded by porcelain-white scars, telangiectasia, hyperpigmentation, and palpable purpura (Fig. 1). Livedo reticularis with an irregular pattern was present on the lower and upper limbs. Arterial pulses in the lower extremities were full and symmetric, and there was no edema. There was no clinical evidence of arthritis.

A skin biopsy from a palpable purpuric lesion showed endothelial swelling and focal hyalinization of the walls of small dermal vessels with intraluminal thrombosis of the whole lumina without an inflammatory infiltrate or leukocytoclasia, aspects compatible with segmental hyalinizing vasculitis (Figs 2 and 3). No immunoglobulin or complement deposition was found on direct immunofluorescence.

A biopsy of the oral mucosa revealed, in a single lobule of a salivary gland, a dense mononuclear infiltrate around an intralobular duct. Schirmer’s test values were 0 mm for the left eye and 2 mm for the right eye, results suggestive of SS. Non-invasive venous Doppler, chest X-ray, and abdominal scan were normal.

Routine and other complementary laboratory blood tests, including platelet count, prothrombin time, activated partial thromboplastin time, fibrinogen and fibrin degradation products, electrophoretic proteinogram, immunoglobulin fractions, C3 and C4, circulating immune complexes, cryoglobulins, antinuclear (ANA) and antineutrophilic cytoplasmic (ANCA) antibodies, venereal disease research laboratory (VDRL) test, C-reactive protein, erythrocyte sedimentation rate, and hepatitis B and C serologies were negative or within the normal range, except for a repeatedly positive rheumatoid factor (50 IU/mL). With a clinical and histologic diagnosis of LV, we further evaluated the following prothrombotic factors: antithrombin III, proteins C and S, factors V, VIII, IX, factor V G1691A (factor V Leiden), prothrombin G20210A, and MTHFR. The patient was homozygous for the C677T mutation in the MTHFR gene. Homocysteinemia measured 4 months later, and after stopping folic acid supplements for 3 weeks, was within normal limits.

Treatment was initiated with oral methylprednisolone 32 mg/day and, once the coagulation studies were concluded, 3 weeks later, subcutaneous enoxaparin 20 mg/day and oral folic acid 5 mg/day. As pain subsided rapidly and ulcer healing progressed, steroid was progressively tapered. At 4 months, with complete resolution of the ulcers (Fig. 4), steroid was stopped and enoxaparin was replaced by warfarin. Six months thereafter, in the summer of 2005, although the
The association of LV with systemic diseases, such as scleroderma, lupus erythematosus, cryoglobulinemia, and antiphospholipid syndrome, may be the result of an underlying endothelial aggression or coagulation disorder that frequently is associated with these diseases. No reference has been found in the literature concerning the association of LV and SS, and, although it is an autoimmune disease, the association of SS with antiphospholipid antibodies or coagulation defects has not been reported. Cutaneous vasculitis with palpable purpura occurs frequently in SS, especially in Ro-positive SS (not the case in our patient), and is a result of small vessel leukocytoclastic vasculitis or hypocomplementemic urticarial vasculitis with lymphocytic perivascular inflammation, not LV. Therefore, this case may just be a coincidental association.

Although many cases of LV are still considered to be idiopathic, this may be the result of an incomplete study of the coagulation parameters or of the necessity of the association of minor disorders of coagulation in the same patient. In our case, we found a homozygous state for mutation of the enzyme MTHFR. This enzyme shunts methyl groups from DNA synthesis to the methylation pathways, therefore converting homocysteine to methionine. In C677T MTHFR mutation, a C moiety is substituted for a T moiety at nucleotide 677 in the encoding region of the MTHFR gene, converting the codon for alanine to valine. Therefore, the final protein has decreased enzyme activity and, consequently, patients develop a mild or moderate hyperhomocysteinemia. Nevertheless, several factors, including folic acid intake, may influence plasma homocysteine levels, as may have occurred in our patient, who was homozygous for the C677T MTHFR mutation but had a normal value for homocysteine 3 weeks after stopping folic acid supplements. Both hyperhomocysteinemia and the C677T MTHFR mutation have been associated with an increased risk of venous and arterial thrombosis in different organs, although in some studies this is not so evident, and some authors have suggested that other concomitant minor thrombophilic disorders or a low folate status may be necessary to increase the risk of arterial or venous thrombosis.

The mechanism of the effect of homocysteine on coagulation is not completely understood, but in vitro studies have shown that it interferes with the fibrinolytic and anticoagulant system and may damage endothelial cells.

The therapy of LV is usually difficult and disappointing, as shown by the wide list of treatments reported with very irregular results: dapsone, corticosteroids, acetylsalicylic acid and other platelet aggregation inhibitors, nicotinic acid, pentoxifylline, the S2 serotoninergic blocker ketanserin, hyperbaric oxygen, danazol and other fibrinolytic agents, prostacyclin analogs such as iloprost, IVIG, and psoralen plus UV-A (PUVA). Our case, previously submitted to several of these treatments without benefit, represents another example of the difficulty of LV therapy. In this case, as in previously reported cases, a good response to LMWH makes this a potential therapeutic possibility in the treatment of LV, even in the absence of detectable coagulation defects. Vitamin K antagonists may be used to replace
LMWH in some cases, as occurred in our patient whose ulcers remained completely healed for 6 months.

In LV, it is advisable to perform broad hematologic tests to uncover the presence of a possible thrombogenic factor, associated or not with an underlying autoimmune disorder. Even when not documented by the presently available laboratory methods, we stress the importance of antithrombotic treatments (anticoagulant and fibrinolytic therapies) in the healing of skin ulcers of LV. In the present case, as there was a homozygous state for the C677T mutation of MTHFR, in addition to persistent anticoagulation, folic acid supplementation was advised in order to prevent thrombotic events in other organs.

References