Ulcerative livedoid vasculopathy responding to clopidogrel

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INTRODUCTION

Livedoid vasculopathy (LV) is a thrombotic, noninflammatory disorder that typically affects the lower extremities. Treatments for LV are widely varied and can be difficult to obtain because of high cost or lack of availability. We present a case of LV with ulcers in an adult woman successfully treated with clopidogrel, a widely available antiplatelet agent. Our case suggests that clopidogrel can be an effective and accessible treatment option for ulcerative LV.

CASE REPORT

A 35-year-old woman with interstitial lung disease (ILD) and undifferentiated connective tissue disease presenting for an inpatient dermatology consult had a painful rash on her bilateral lower extremities. The rash started 2 months before presentation as exquisitely tender red macules on bilateral medial arches of the feet, which progressed to retiform, purpuric patches and finally to ulcers (Fig 1). Before hospitalization, her primary care physician had treated her with doxycycline for suspected folliculitis.

Two punch biopsies of the left foot found hyalinized thrombi occluding small dermal vessels with scant inflammation suggestive of LV (Fig 2). She underwent workup for hypercoagulable and autoimmune disorders and was found to have a weakly positive anti-alanyl-tRNA synthetase (anti-PL-12), positive anti-SSA antibodies, and low complement. She was heterozygous for a methylene-tetrahydrofolate reductase A1298C mutation with 80% of normal enzyme activity, which was determined not to be a risk factor for hyperhomocysteinemia. She had normal factor V Leiden, negative antiphospholipid, antinuclear, anti-Smith, antiribonucleoprotein, anti-Jo-1, and antineutrophil cytoplasmic antibodies. Erythrocyte sedimentation rate, creatine kinase, and cryoglobulins were normal. For ILD, prednisone was continued, with daily doses as high as 80 mg/d. Azathioprine, 50 mg/d, and dapsone, 100 mg/d, were started at discharge. Low-dose aspirin was also started without improvement of her ulcers after 2 months.

Abbreviations used:

ILD: interstitial lung disease
IVIG: intravenous immunoglobulin
LV: livedoid vasculopathy

At her outpatient dermatology follow-up appointment 2 months after discharge, there were scattered ulcerations ranging from 1.5 to 5 cm on her bilateral feet and ankles with erythematous, rolled borders (Fig 3). Clopidogrel, 75 mg once daily, was started, and aspirin was discontinued. One month later, there was marked improvement of her ulcers. Complete re-epithelialization occurred 4 months after starting clopidogrel (Fig 4). During clopidogrel treatment, she had a 3-week break from clopidogrel because of a syncopal episode. During this interval, she reported flaring of her symptoms with new leg lesions and increased pain. She was restarted on clopidogrel with the approval of her primary care physician, and noted resolution of her symptoms. She continued prednisone; azathioprine, which increased as high as 200 mg/d; and dapsone for her ILD. At 1-year follow-up, the patient was continued on 75 mg clopidogrel daily and has not had recurrence of her ulcers.

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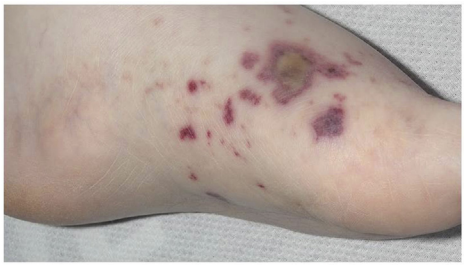

Fig 1. Stellate, noninflammatory retiform purpuric patches with central necrosis on the medial arch of the left foot at the time of hospital admission.

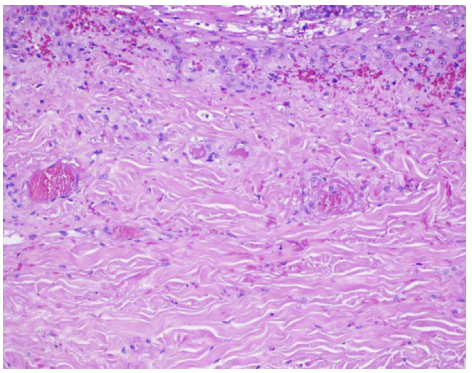

Fig 2. Occlusion of the lumina of nearly all small dermal vessels by hyalinized thrombi, with overlying epidermal necrosis and scant karyorrhectic nuclear debris.

DISCUSSION

This case provides an example of a therapeutic response to clopidogrel in a patient with ulcerative LV. LV has a 3:1 female predominance with an average age of diagnosis of 32 years.[1] Characteristic skin changes include atrophie blanche and livedo reticularis. The pathology is found at the level of the dermis involving blood vessels. It may be associated with autoimmune diseases such as systemic lupus erythematosus and a variety of hypercoagulable disorders, which may be identified on thorough hypercoagulable workup.[2] Differential diagnoses include venous stasis ulcers, systemic vasculitides, peripheral arterial disease, pyoderma gangrenosum, and trauma. Cases of improvement with aspirin, dipyridamole, and bed rest have been published.[3] Additional reports of LV have indicated improvement with anticoagulants (eg, warfarin, heparin, rivaroxaban, tissue plasminogen activator), antimalarials (eg, hydroxychloroquine), immunosuppressants (eg, intravenous immunoglobulin [IVIG], sulfapyridine, dapsone), iloprost, pentoxifylline, psoralens and ultraviolet A, hyperbaric oxygen, and B vitamins including folate supplementation when associated with hyperhomocysteinemia.[4-6]

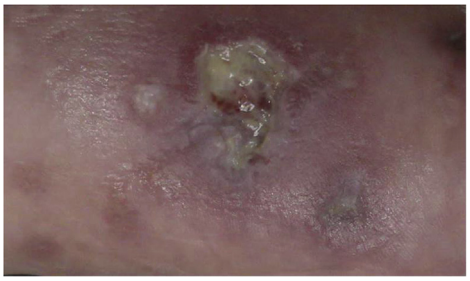

Fig 3. Ulcer with rolled, erythematous borders measuring 1.5 × 2.3 cm on left medial foot 2 months after hospitalization.

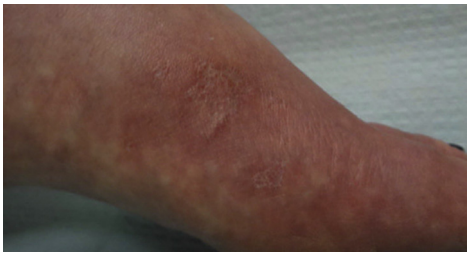

Fig 4. Complete re-epithelialization of ulcers 4 months after starting clopidogrel, 75 mg daily.

Two other cases are reported of successful treatment of LV using clopidogrel with shorter follow-up periods.[1] The 2 patients reported by Poletti et al[1] in Spanish had normal serologic findings and were treated with higher doses of clopidogrel (150 mg/d) for 2 to 3 weeks followed by 75 mg/d for 3 months. Our case is notable in that the patient reported worsening of her skin symptoms while briefly off clopidogrel and improvement in her lesions after restarting clopidogrel. Also, the 1-year follow-up period of our patient with ulcerative LV on clopidogrel is longer than that of these patients.

Clopidogrel is found to improve microcirculation in the skin.[7] It has been used in the treatment of other skin disorders related to poor circulation including venous stasis ulcers.[8] Clopidogrel irreversibly binds to the adenosine diphosphate P2Y12 receptor on the surface of platelets, thereby inhibiting activation of the glycoprotein IIb/IIIa complex. The glycoprotein IIb/IIIa plays an important role in platelet aggregation and its activation is adenosine diphosphate mediated. Although its mechanism of action in LV is not completely characterized, we postulate that the antiplatelet aggregation effects of clopidogrel combat the thrombotic pathology in LV. Major side effects of clopidogrel include hemorrhage, pancytopenia, thrombotic thrombocytopenic purpura, fixed drug eruption, and hypersensitivity reactions. Thus, we recommend obtaining approval from a patient's primary care physician before

starting this drug. Some studies report remission of LV with warfarin or IVIG after little improvement with clopidogrel.[9,10] The patient with definitive improvement with warfarin was found to have an associated prothrombin mutation and presented with a unique finding of tender nodules with fat necrosis in addition to ulcerative LV.[9] In the case series by Bounfour et al,[10] 5 patients with LV were treated with IVIG. Only 1 patient was previously treated with clopidogrel, and this patient was continued on clopidogrel during IVIG treatment. The patient concomitantly treated with clopidogrel was the only patient of the 5 to completely respond without relapse.[10]

We present a case of ulcerative LV that responded well to clopidogrel. Although additive effects from prednisone, dapsone, and azathioprine for our patient's ILD cannot be ruled out, the patient's relapse of her LV when briefly off clopidogrel supports the medication's therapeutic potential. One year after initial presentation, our patient continues to do well on clopidogrel, 75 mg daily, and has not had recurrence of her ulcers. We recommend further studies be performed in larger patient cohorts to determine the efficacy of clopidogrel in LV.

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