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Successful Treatment of Severe Single-Organ Cutaneous Small-Vessel Vasculitis with Pulse Steroid, Cyclophosphamide and Mycophenolic Acid

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Abstract

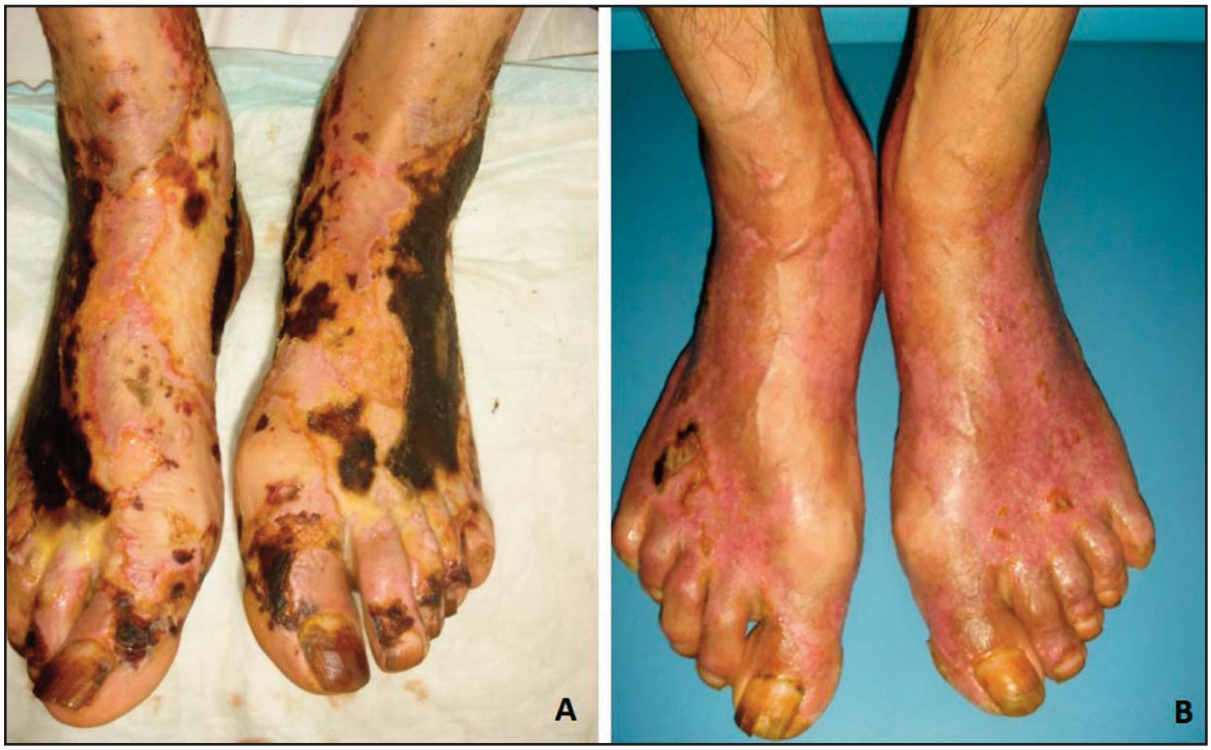
Observation: There is no evidence based recommendation for the treatment of single-organ cutaneous small-vessel vasculitis. Cutaneous vasculitis with massive necrotic skin lesions should be treated with aggressive immunosupressive drugs since necrotic lesions are indicators of mortality and disease relapses according to retrospective studies. Here we report a case of single-organ cutaneous small-vessel vasculitis which was successfully treated with pulse steroid, cyclophosphamide and mycophenolic acid.

Introduction

The 2012 revised International Chapel Hill Consensus Conference (CHCC) Nomenclature of Vasculitides defines single-organ vasculitis as a vasculitis affecting arteries or veins of any size in a single organ, with no features suggesting limited expression of a systemic vasculitis. When confined to the skin, the term single-organ cutaneous small-vessel vasculitis (SoCSVV) is used. If vasculitis developed in association with systemic disease like lupus erythematosus then the term secondary vasculitis is used. Other type vasculitis considering as primary or idiopathic vasculitis. Vasculitis associated with probable etiologies like drugs, infections and malignancy should be called for example cancer-associated vasculitis [**1**]. Up-to-date no placebo-controlled double-blind trials exist and the evidence for efficacy of any therapy in the management of SoCSVV vasculitis. However, European League Against Rheumatism (EULAR) recommended treatment modalities for ANCA-associated vasculitis and polyarteritis nodosa [**2**]. Here we report a case of severe SoCSVV of unknown etiology which was treated with pulse steroid, cyclophosphamide for remission induction therapy as recommended EULAR [**2**] and mycophenolic acid for maintenance therapy.

Case Report

54-year-old male patient hospitalised in dermatology department due to necrotic skin lesions on both feet. Medical history of patient demonstrated that he exposed to multiple insect bites on both feet while he was on beach. Within a few days after the insect bite, hemorrhagic, palpable, bullous lesions evolved which are consequently become a necrotic skin lesions. Dermatological examination revealed massive superficial necrosis on dorsum of the feet and multiple palpable petechial lesions on upper part of legs and upper extremities (**Figures 1A and B**). All vital signs were normal. There



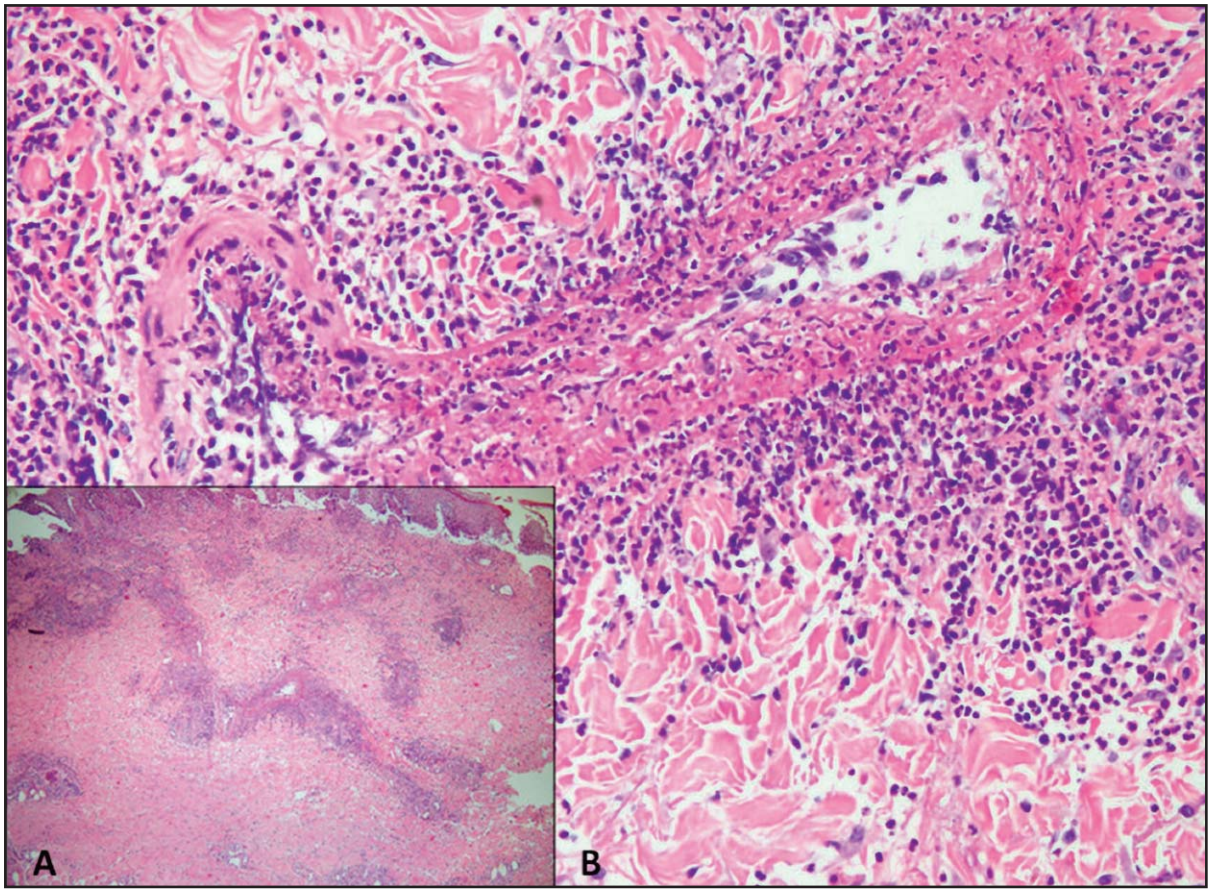
Figures 1A and B. A. Necrotic skin lesions. B. Healed skin after one month of the treatment

was a high morbidity, since our patient was almost immobile, because of painful necrotic lesions. He suffered from diabetes mellitus for five years and panic attack for ten years. He was using alprozolam and metformin with videgliptin combination. No other drugs he used before the development of skin lesions.

Skin biopsy was taken from petechial lesions showed leukocytoclastic vasculitis at the upper and mid dermis. The vessel walls are thickened, perivascular fibrin exudation, neutrophilic infiltration, and leukocytoclasia were prominent. An ulceration at the surface was seen. Direct immunofluorescence examination was negative. (**Figures 2A and B**). Routine blood test showed highly elevated acute fase reactans. CRP was 20 mg/dL. Complement level was normal. But D-dimer level was very high (>4550 µg/L FEU) which thought to be the indicator of trombosis secondarily to vasculitis. INR also was slightly elevated. Platelet count was normal. Doppler ultrosongraphy of areterial and venous system was normal. Malignancy screening was negative. There were not any source of infection which may cause vasculitis. ANCA and other autoimmune markers were negative. Thyroid function test was abnormal due to euthyroid sick syndrome which later turned to the normal ranges. There was no systemic involvement of vasculitis especially renal and gastrointestinal system. So, patient was diagnosed as primary SoCSVV. As a treatment, metilprednisolone 750 mg/d administered for five days. On two ocassions, intravenous cyclophosphamide at a dose of 15 mg/kg per week administered. Steroid treatment continued with methylprednisolon 60mg/day for one month and then gradually tapered. As a steroid sparing agent we started paralelly to steroid treatment mycophenolic acid 180 mg twice a day. Azathioprine abandoned due to bone morrow supression in our patient. Aspirin and enoxiparin was also used as a supportive treatment. A few days after the pulse therapy, the patient exposed to delirium attack which brought to control with holoperidol and diazepam combination. Central nervous system involvement of vasculitis also ruled out. So, aggrevation of pre-existent psychiatric problems due to high dose steroid treatment was thought. There were not any complications related to pulse therapy except delirium. After the month from the day of the treatment, the skin lesions almost completely healed (**Figure 1B**). Mycofenolic acid was continued with minimal dosage for one year after steroid cessation as a monotherapy and relapses did not occure.

Discussion

There is no evidence based recommendation for SoCSVV treatment [**3**]. Management modalities for the SoCSVV based on case reports series and personel experiences. First line therapy for SoCSVV are antihistaminics,



Figures 2A and B. A. The biopsy showes subepidermal blister and necrotizing vasculitis (H&E x40)
B. Perivascular fibrin exudation, neutrophilic infiltration and leukocytoclasia (H&E x 200)

NSAID and corticosteroid in 0.5-1 mg/kg daily dosage. In refractory cases, colchicium, hydroxycloroquine, dapson, azathioprine, cyclosporine, cyclophosphamide and methotrexate can be used [3]. Reports regarding mycophenolic acid in the treatment of SoCSVV is limited [4]. Pulse steroid and cyclophosphamide are usually given in organ involvement of vasculitis, especially ANCA-associated necrotizing vasculitis for remission induction therapy [2]. In our case, the severity of skin lesions, abnormal laboratory indicators and constantly evolving new petechial lesions on intact skin, made us to think about agressive immunotherapy. Recently published retrospective analyses of vasculitic patients, demonstrate that cutanous necrosis is a rare clinical manifestation of cutaneous vasculitis and it is associated with increased risk of mortality and disease relapses [5]. That is why, cutaneous vasculitis with massive necrotic skin lesions should be treated with potent immunosupresive drugs. Based on these knowledge, patient was treated with pulse steroid, cyclophosphamide for remission induction and mycophenolic acid for maintenance therapy.

Moreover, patient described multiple insect bite lesions before the vasculitis onset. However, clinically and histopathologically it was not proved. We were unable to observe previous lesions. In the literature there are limited reports regarding insect bite associated vasculitis [6]. In this context, patient was diagnosed as an idiopathic SoCSSV.

Conclusion

Primary SoCSVV usually has a benign course and well respond to the first and second line therapies. However, in acute onset SoCSVV with massive necrotic lesions, pulse steroid treatment in combination with cyclophosphamide for the remission induction and mycofenolic acid for the maintenance therapy should be considered.

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