Botulinum toxin-A: A novel treatment for livedoid vasculopathy

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INTRODUCTION

Livedoid vasculopathy (LV) is a rare cutaneous condition that manifests as painful, chronic lower extremity ulcers.[1] We report a case of refractory LV treated with botulinum toxin-A (BTX-A), in which ulcer healing and disease stabilization were observed. To our knowledge, there are no other reports in the literature describing BTX-A as a potential therapy for LV.

Abbreviations used:

BTX-A: botulinum toxin-A
IVIG: intravenous immunoglobulin
LV: livedoid vasculopathy

CASE REPORT

A 20-year-old woman presented with an 8-month history of painful ulcers that would slowly heal as white scars on her bilateral lower extremities. She was otherwise healthy and reported 4/10 pain localized to the active ulcers, 8/10 lower extremity neuropathic pain, and edema with prolonged standing. The examination demonstrated retiform purpuric patches, crusted purple papules, and superficial ulcers associated with white ivory plaques on her bilateral malleoli and dorsal aspect of the feet (Fig 1). Punch biopsies supported the diagnosis of LV (Fig 2). No underlying thrombophilia or autoimmune connective tissue disease was identified. Lower extremity ankle-brachial indices, venous ultrasound, Doppler, electromyography, and nerve conduction studies were normal bilaterally.

The patient's previous treatments included monotherapy with acetylsalicylic acid at 325 mg daily for 1 month, combination therapy of 325 mg acetylsalicylic acid and 10 mg rivaroxaban, and high-dose intravenous immunoglobulin (IVIG) infusions at 2 mg/kg. However, the patient endorsed persistent ulcers and diffuse neuropathic pain (Fig 3). She was also trialed on various analgesic regimens, including gabapentin, amitriptyline, topiramate, duloxetine, tramadol, and acupuncture with little success.

Although the neurovascular workup was normal, her neurologist suspected LV-induced small fiber neuropathy and recommended BTX-A. BTX-A was diluted with bacteriostatic normal saline to a final concentration of 4 units per 0.1cc. She received intradermal injections of 50 units to her left malleolus, with repeat treatment of 200 units to her bilateral malleolar and dorsal aspect of the feet 2 weeks later. Injections were administered in a 1cm grid around active ulcers. The patient tolerated the injections well; although, she was noted to have a minor cold roller burn following her first injection (Fig 4).

Within 2 to 3 weeks after initial BTX-A therapy, the patient reported improvement directly over her ulcers with no new lesions (Fig 4). At 4 to 6 weeks postinjection, there were no active ulcers or lesional skin pain; however, diffuse neuropathic pain was 7/10. At approximately 3 months post-BTX-A therapy, the patient demonstrated new ulcers despite anticoagulation resumption, completion of 4 IVIG cycles, and hyperbaric oxygen treatment. She received a third

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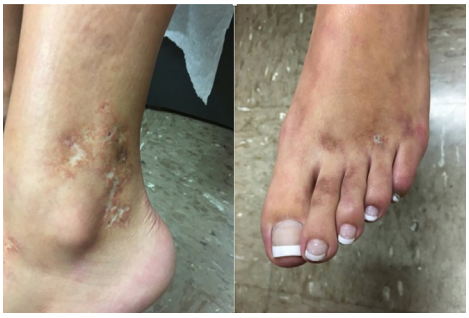

Fig 1. Photograph of lesions at presentation, before disease progression or initiation of any treatment.

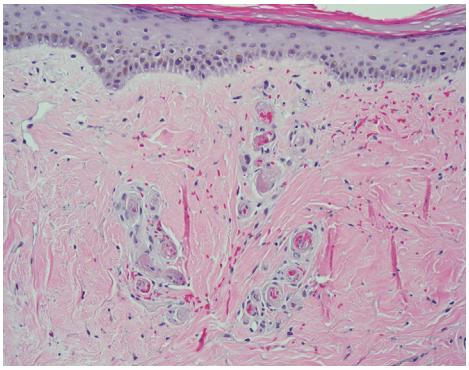

Fig 2. Punch biopsy demonstrating fibrinoid material within walls of papillary and reticular dermal vessels along with intraluminal hyaline thrombi. There is a mild perivascular lymphocytic infiltrate without evidence of leukocytoclastic vasculitis.

treatment with 200 units of BTX-A. At 1 month follow-up, she again showed ulcer healing and was able to resume wearing compression stockings and aquatic therapy. Throughout her BTX-A treatment course, the patient had a reduced analgesic requirement along with improved strength, endurance, and mobility.

Laboratory reports demonstrated hepatitis B exposure or prior infection with negative hepatitis B viral DNA and high titer antinuclear antibody screen at 1:1280 with subsequent negative serologies. Negative or normal studies are as follows: protein C and S, resistance, anti-thrombin 3, lupus panel (cardiolipin, double stranded DNA, anti-Smith, anti-ribonucleoprotein, anti-Ro/La, anti-Jo-1, cyclic citrullinated peptide), complement (C3/C4 and CH50), B2-glycoprotein, cryoglobulins, antineutrophil cytoplasmic antibodies (P-ANCA/C-ANCA and atypical ANCA), myeloperoxidase, proteinase 3, erythrocyte sedimentation rate, urinalysis, comprehensive metabolic panel to include liver function test, complete blood cell count with differential, HIV, serum protein electrophoresis/urine protein electrophoresis, von Willebrand Factor, and coagulation panel.

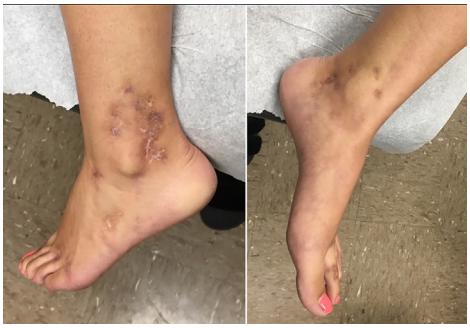

Fig 3. Photograph of the patient's lesions after initiation of intravenous immunoglobulin and anticoagulation, but before treatment with botulinum toxin-A

DISCUSSION

LV is a rare disease hypothesized to be because of a vaso-occlusive and prothrombotic disease state within the cutaneous microcirculation.[2] Only 50% of cases have an identifiable underlying thrombophilia, with a large proportion of the cases considered idiopathic after extensive evaluation.[2,3] In the absence of underlying coagulopathy or autoimmune connective tissue disease, treatment goals are to stabilize the disease, reduce pain, and prevent disease recurrence. Treatment with anticoagulation therapy is the most common monotherapy, but other modalities include corticosteroids, IVIG, and antiplatelet therapy.[1]

Our patient's clinical response to BTX-A was chronologically consistent with other ulcerative conditions treated in the same manner, where >50% of subjects reported improvement in pain and ulcer healing 1 month following a single treatment.[4]

BTX-A has shown promising results in treating chronic ulcers associated with autoimmune connective tissue diseases with a proposed mechanism of inhibiting sympathetic vasoconstriction and vasospasm.[5,6] Therefore, we propose that BTX-A-induced smooth muscle vasodilation may counter the cutaneous vasoocclusion seen in LV. Furthermore, BTX-A has been shown to augment wound healing during the inflammatory, proliferative, and remodeling phases of ulcers that are caused by a variety of other etiologies.[7]

Because of concomitant treatment with IVIG and resumption of rivaroxaban, we cannot quantify the contribution of BTX-A to ulcer healing alone but suspect an added therapeutic benefit. Based on available evidence, IVIG is felt to exert anticoagulation and antiinflammatory properties; however, the degree of clinical improvement noted at our patient's follow-up was not consistent with the improvement noted on 2 cycles of IVIG alone.[1] Based on a systematic review of 32 patients with LV treated

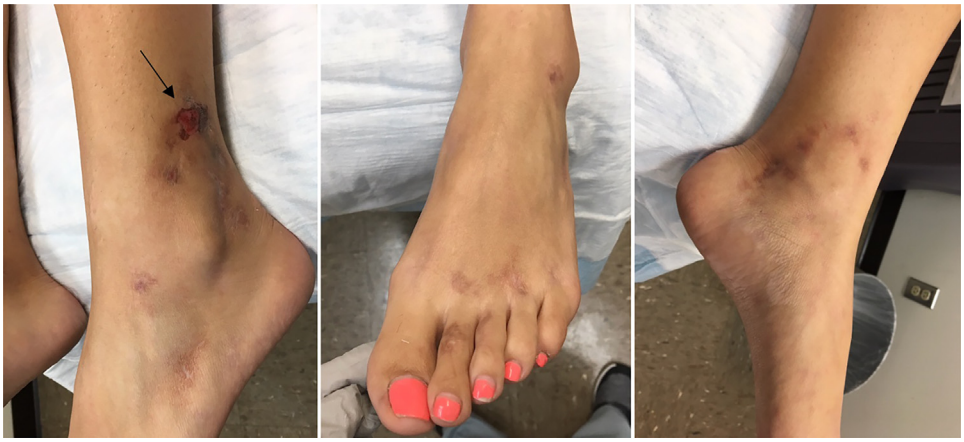

Fig 4. Photograph of the patient's lesions 2 weeks after initiating treatment with botulinum toxin-A. The first injection was complicated by a small superficial erosion from a cold roller burn used during the procedure (*black arrow*).

with IVIG and anticoagulation, approximately 68% of patients experienced healing and reduction of ulcer pain after an average of 4.4 cycles.[8] Moreover, the patient had disease recrudescence 3 months post-BTX-A injection, at the expected time that the therapeutic effects would be waning.

Small fiber peripheral neuropathy may be a common but underreported extracutaneous complication of LV that can persist after ulcer healing.[3] BTX-A is well described as an effective therapy for many types of neuropathic pain.[9] Analgesic effects have been attributed to the inhibition of the release of pain mediators from both motor and sensory neurons, blockage of pain-related neuropeptides, and reduction of neurotransmitters that perpetuate inflammation.[9]

A multifaceted approach to pain must be considered in the management of LV because various factors and pathways are implicated in the experience of pain. It is unclear why our patient saw a notable improvement in cutaneous pain associated with ulcer healing, but with no significant improvement in chronic neuropathic pain. Given its subjective nature, the lack of incorporation of a more objective and qualitative measure, such as the neuropathy pain scale, is a limitation of this case. The standard visual analog scale does not adequately stratify pain types (ie, sharp, hot, dull, cold, deep, surface, etc.) and was unlikely to be sensitive enough to detect subtle changes. Moreover, using an injection protocol that is tailored for periphery neuropathy as opposed to injecting lesional around ulcers, may have shown more profound results in our patient. However, the clinically observed ulcer healing, disease stabilization, and decreased lesional pain, as characterized by reduced analgesic use and improved functional mobility, warrants further consideration of BTX-A as a novel and well-tolerated therapeutic approach in LV. Further studies are needed to confirm the efficacy of BTX-A for chronic ulcers, cutaneous and neuropathic pain, optimal injection protocols, and long-term safety and durability in patients with LV.

Conflicts of interest

None disclosed.

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