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Botulinum toxin for treatment of Raynaud phenomenon in CREST syndrome

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Abstract

Calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia (CREST) syndrome is a form of a rare, clinical subtype of systemic sclerosis, known as *limited* systemic sclerosis. Limited systemic sclerosis, including CREST syndrome, manifests as fibrotic skin changes restricted to the hands and face, with vascular, musculoskeletal, and visceral involvement. We present a case of a 75-year-old woman with a longstanding history of CREST syndrome complicated by a digital ulceration and persistent pain associated with recalcitrant Raynaud phenomenon. After failing a number of first-line pharmacologic therapies such as diltiazem, sildenafil, and topical nitropaste, the patient was started on a trial of botulinum toxin for the left second digit, with 10 unit injections into both webspaces for a total of 20 units. Following injection, the patient reported no further baseline pain in the affected finger and an over fifty-percent improvement in discomfort with manipulation of the digit at a follow-up time of one week. The ulceration started healing within the following three weeks. This result was maintained at a follow-up time of six weeks.

Keywords: CREST syndrome, limited systemic sclerosis, Raynaud phenomenon, botulinum toxin

Introduction

Blood vessel constriction of the fingers and toes, known as Raynaud phenomenon (RP), is one of the most common and earliest signs of calcinosis,

Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia (CREST) syndrome. Because RP in CREST syndrome is not only related to vasospasm, but also to structural defects in the vasculature, complications such as ulcerations or even gangrene can arise [1, 2]. We report a case of a CREST patient whose digital ulceration from RP was successfully treated with botulinum toxin injections.

Case Synopsis

A 75-year-old woman with a history of dysphagia, atrial fibrillation, pulmonary hypertension, and congestive heart failure presented to the dermatology clinic for evaluation of persistent pain and white-to-purple discoloration over her fingers for many years. Over the last several months, she developed a crusted ulceration of the left second finger and nearly constant baseline pain. The patient tried warming, electric gloves, diltiazem, topical nitropaste, and sildenafil but felt no significant symptomatic relief. She also reported subcutaneous nodules over her knees and elbows that were sometimes tender and extruded a white material. Review of systems was otherwise negative.

On physical examination, there were several circular, erythematous, blanching macules on the face. The fingers were tapered at the ends and diffusely white-to-purple in color (**Figure 1**). The tip of her left second digit had a crusted ulceration that was tender to palpation (**Figure 2**). There was no hardening or thickening of the skin or dyspigmentation of the arms or legs. On the right knee and elbows, there



Figure 1: Dorsal hands with sclerodactyly

were tender, white nodules with a background of erythema and a few areas of white-chalky-material extrusions. A complete blood count and liver function tests were normal. Rheumatoid factor and anti-cyclic citrullinated peptide antibody were within normal limits. Antinuclear antibody was 1:1280 and demonstrated a centromere pattern; anti-centromere antibody was elevated (>8.0); anti-topoisomerase antibody was within normal limits. No biopsies were performed.

Case Discussion

CREST syndrome belongs to a rare, clinical subtype of systemic sclerosis, known as *limited* systemic sclerosis. Systemic sclerosis (SSc), commonly known as scleroderma, is an autoimmune connective tissue disease of unknown etiology that is characterized by thickening of the skin, vasculature, musculature, and internal organs. The *limited* and *diffuse* cutaneous SSc (lcSSc and dcSSc) subtypes are differentiated by



Figure 2: Left second digit with crusted ulceration

extent of skin involvement and pattern of visceral involvement. LcSSc, which includes CREST syndrome, manifests as fibrotic skin changes that are typically restricted to the hands, face, and neck, with mild-to-moderate delayed internal fibrosis, mainly of the vasculature [3].

A diagnosis of SSc is based on a confluence of clinical and laboratory findings. According to the most recent 2013 classification scheme, SSc is confirmed by either skin thickening extending proximal to metacarpophalangeal (MCP) joints (major criterion), or a significant combination of skin thickening of the fingers distal to MCP joints, fingertip lesions, telangiectasias, abnormal nailfold capillaries, interstitial lung disease or pulmonary arterial hypertension, Raynaud phenomenon, and one positive SSc-specific autoantibody (anti-centromere or centromere pattern on antinuclear antibody, anti-topoisomerase, and anti-RNA polymerase III antibodies), (minor criteria), [4]. Apart from serving as diagnostic criteria, the three most common SSc-

related autoantibodies impart important clinical information. For example, anti-centromere antibodies seen in our patient are reliable indicators of lcSSc and prolonged survival compared with dcSSc, and confer an increased risk of developing isolated pulmonary arterial hypertension in the absence of interstitial lung disease [5, 6].

Raynaud phenomenon (RP) is one of the most common and earliest manifestations of SSc (90% of patients with SSc have RP and 12.5% of patients with RP develop definitive SSc), [2]. Additionally, SSc represents one of the leading causes of secondary RP in association with an underlying disease process. The lcSSc patient often has RP for many years before the manifestation of other SSc features, whereas the dcSSc patient has an abrupt onset of RP often coinciding with SSc features [3]. Secondary RP in SSc includes not only digital vasospasm but also structural defects in the vascular supply owing to angiogenesis defects, intimal proliferation, and luminal obstruction. Therefore, the associated ischemia can be severe and results in acral ulceration and loss of function [1, 7, 8].

Treatments for SSc are focused primarily on addressing visceral involvement and therapeutic interventions for cutaneous manifestations are limited [9]. Treatment modalities for Raynaud phenomenon are aimed at preventing exaggerated vasospasm, encouraging vasodilatory response, and increasing blood flow [10]. First-line therapy is behavioral and involves warming the hands and avoiding vasospasm or vasoconstrictive triggers (including medications such as beta blockers). Second-line is vasodilatory pharmacologic therapy. Calcium channel blockers, particularly nifedipine and amlodipine, have been the most widely used medications. The use of other classes of medications include angiotensin II inhibitors, selective serotonin reuptake inhibitors, ACE inhibitors, alpha-blockers,

oral and topical nitrates, low-dose aspirin, intravenous prostacyclin, endothelin receptor blockers, and phosphodiesterase inhibitors [1, 7].

Recently, botulinum toxin has been used as a means to relieve symptoms of RP [10, 11]. Although botulinum toxin's main mechanism of action — inhibition of presynaptic acetylcholine release — likely plays a role in reducing RP symptomatology, it is believed that the toxin may also work by preventing sympathetic vasoconstriction of vascular smooth muscle through similar inhibition of norepinephrine vesicle release and by blocking pain transmission peptides that activate the α_2 -adrenoreceptor C-fiber nociceptors [10, 12-15]. Though larger controlled trials are needed to establish efficacy, a recent review found botulinum toxin led to overall improvement in patient pain, increased blood flow, and reduction in soft tissue ulceration [10]. We injected our patient with 10 units of botulinum toxin into both sides of the webspaces of the ulcerated left second digit. Following injection, the patient reported no further baseline pain in the affected finger and an over fifty-percent improvement in discomfort with manipulation of the digit at a follow-up time of one week. The ulceration started healing within the following three weeks. This result was maintained at a follow-up time of six weeks.

Conclusion

Digital ulceration and persistent pain is associated with recalcitrant Raynaud phenomenon, a common sequela of CREST syndrome, or limited systemic sclerosis. After failing a number of first-line pharmacologic therapies, botulinum toxin injected into the webspaces of our patient's ulcerated digit resulted in symptomatic improvement and ulcer healing.

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