

Case Report

# Effectiveness of botulinum toxin A in treatment of refractory erythromelalgia

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## Abstract

Erythromelalgia is characterized by intense burning pain, erythema, and heat in affected areas after precipitating factors such as warm temperature or stress. It is refractory to treatment in some situations. We describe a woman with adenocarcinoma of the lung and medically refractory erythromelalgia. The symptoms of erythromelalgia presented as refractory to any medical treatment. Due to the unresponsive nature of her condition, botulinum toxin type A (onabotulinumtoxin A) was injected over both of her cheeks, periodically for six cycles. Her symptoms responded dramatically to subcutaneous and intradermal injection of botulinum toxin type A. Repetitive injection demonstrated consistent and reproducible responses, and the efficacy was maintained for approximately 1 month. No adverse effects or complications were noted. Botulinum toxin type A might be safe and effective as an alternative treatment for refractory erythromelalgia, but further large-scale studies are required.

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## 1. Introduction

Erythromelalgia is a small-fiber neuropathy<sup>1</sup> characterized by intense burning pain, erythema, and warmth in the affected areas.<sup>2</sup> Symptoms are triggered by heat or sunlight exposure, and can be alleviated by cooling of the affected area. Treatment for this disorder has proven difficult and involves multiple approaches. We describe a patient with erythromelalgia who was medically refractory but responded dramatically to onabotulinumtoxin A injection.

## 2. Case report

A 58-year-old housewife had suffered intermittent hot flushing and burning pain over her face and all four limbs

since 2005. The symptoms were exacerbated by warm temperatures, exercise, or sunlight exposure, and relieved by cooling of the affected area. Physical and neurologic examinations revealed severe erythema, local heat, and allodynia over the affected areas. Postmenopausal syndrome was suspected initially, but no satisfactory response to hormone therapy was noted. Rosacea had also been considered, but there was no patient response to tetracycline and prednisolone.

A full diagnostic work-up, including assessment of thyroid function, hepatitis C testing, plasma catecholamine, urine 5-hydroxyindoleacetic acid, and vanillylmandelic acid levels, as well as autoimmune profiles including antinuclear antibody, double-stranded DNA, complements, immunoelectrophoresis, cryoglobulin, rheumatic factor, anti-SS-A/SS-B, and anti-Jo-1 antibody were all unrevealing. Nerve conduction studies were normal. A skin biopsy found decreased intraepidermal nerve fiber density (5.23 fibers/mm) (Fig. 1A). The patient was diagnosed with erythromelalgia. In 2009, she was then diagnosed with adenocarcinoma of

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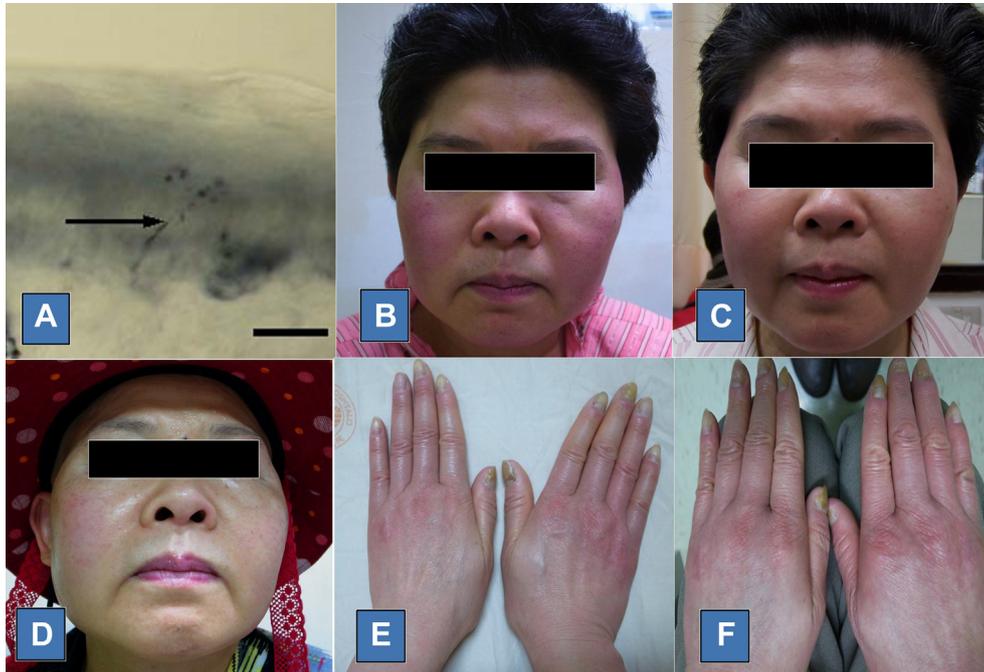


Fig. 1. Photographs of the patient's erythromelalgia during the course of treatment and the skin biopsy. (A) Skin biopsies were immunostained with antiprotein gene product 9.5 (PGP9.5). Epidermal innervation was reduced, with only some visible intraepidermal nerves (arrow). (B) Pretreatment. The patient suffered severe painful erythema of her face. (C) After treatment with the first subcutaneous injection of onabotulinumtoxin A. Facial flushing improved dramatically. (D) After treatment with the fourth injection of onabotulinumtoxin A. The improvement was still significant. The patient was wearing a hat because she felt embarrassed by her chemotherapy-related alopecia. (E) Pretreatment. Erythema of both hands. (F) Post-chemotherapy. There was no notable difference in the erythema of the hands.

the lung. She underwent surgery and chemotherapy with paclitaxel and cisplatin. There was no tumor recurrence until August 2010.

The patient's symptoms of erythromelalgia exacerbated and became excruciating [verbal numeric scale (VNS) 10/10] from January, 2010 (Fig. 1B and E). Temporary relief of symptoms was achieved by immersion of her face in ice water even during the cold winter months. Treatments including escitalopram, propranolol, alprazolam, gabapentin, aspirin, prednisolone, amitriptyline, venlafaxine, duloxetine, mexiletine, or combinations of these drugs were all ineffective. Given the refractoriness of symptoms and the nature of the disease, the patient asked for potential off-label therapeutic choices for neuropathic pain.

Based on pre-existing evidence for botulinum toxin type A in the treatment of neuropathic pain<sup>3</sup> and one successful experience in treating idiopathic facial flushing,<sup>4</sup> we considered that botulinum toxin A injection might be effective in reducing or even eradicating her symptoms. After thorough discussion with the patient about the treatment paradigms and potential adverse effects, she decided to receive the treatment and provided written informed consent. Botulinum toxin type A (onabotulinumtoxin A) injection was then administered in an effort to relieve the patient from her substantial suffering.

Initially, the patient received 12.5 U of onabotulinumtoxin A in 10 locations (1 cm<sup>2</sup> per grid) on each cheek subcutaneously. At 1 week postinjection, the improvement in facial flushing and pain was remarkable (VNS 3/10) (Fig. 1C). No

further medication was needed. The symptoms relapsed 1 month later after intense sunlight exposure. The patient received two further injections at twice the dose given in the initial treatment, which effectively abated her symptoms (VNS 0–2/10) for 4–6 weeks. However, metastatic lung cancer was noted in August 2010. She received surgery and another course of chemotherapy. The fourth injection of onabotulinumtoxin A intradermally (50 U on each cheek) was provided in September 2010. Her symptoms improved greatly, which lasted for 2 months (Fig. 1D). To prevent the development of antbotulinum toxin antibodies, the interinjection interval was prolonged to 3 months for subsequent injections. The patient tolerated all the therapeutic procedures well. A total of six cycles of onabotulinumtoxin A injection was administered. No adverse effects or complications were noted during the subsequent 1.5-year therapeutic course.

### 3. Discussion

Our patient fulfilled the diagnostic criteria of erythromelalgia—burning extremity pain, pain aggravated by warming, pain relieved by cooling, erythema of the affected skin, and increased temperature of the affected skin.<sup>1</sup> The skin biopsy from our patient revealed reduced intraepidermal nerve fiber density (5.23 fibers/mm), which was also consistent with prior studies.<sup>1,5</sup>

We hypothesized that the burning pain and allodynia associated with erythromelalgia were essentially neuropathic pain, and the erythema and local heat were induced by

intense neurogenic inflammation. Onabotulinumtoxin A was reportedly effective in neuropathic pain,<sup>3</sup> and we extrapolated that these results could benefit our patient. The effectiveness might be mediated through an inhibition of peripheral and central sensitization by blocking the release of proinflammatory neurotransmitters, such as calcitonin gene-related peptide, substance P, and glutamate, etc.<sup>4,6</sup> Recent studies modeling neuropathic pain with a local injection of capsaicin provide circumstantial support.<sup>7</sup>

In our study, we used a VNS, which is a well-validated and reliable rating scale for pain, to evaluate the efficacy of the onabotulinumtoxin A injection.<sup>8</sup> The other objective index was the change in skin color, which appeared in concordance with the pain, as illustrated in Fig. 1. Transcutaneous tissue oximetry and laser Doppler flowmetry are more objective assessments for the microcirculation and are expected to provide more information<sup>9</sup>; however, these tools were not available in our clinical practice.

Based on the time course, electrodiagnostic study, and histopathology, chemotherapy-related peripheral neuropathy is not likely the culprit for our patient's symptoms.<sup>10</sup> Treatment for recurrent tumor might contribute to the prolonged remission, but could not explain the responsiveness of prior onabotulinumtoxin A injections. In addition, the noninjected hands showed no obvious improvement after chemotherapy (Fig. 1F).

We proposed that onabotulinumtoxin A might serve as an alternative approach for patients with refractory erythromelalgia. Further randomized trials are needed to systematically assess the efficacy and safety of onabotulinumtoxin A in treating refractory erythromelalgia.

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