A Rare Case of Refractory Erythromelalgia Managed by Botulinum Toxin A

Dear Editor,

Erythromelalgia is a rare dermatological condition with female preponderance, characterized by pain, erythema, and swelling usually in the extremities of the body which usually get relieved by elevating the limbs or cooling. Primary erythromelalgia is due to autosomal dominant mutation in the *SCN9A* gene, which is responsible for voltage-gated sodium channels expressed on small nociceptive neurons, which is crucial for pain perception. Secondary erythromelalgia is due to various underlying acquired causes.[1] Erythromelalgia is frustrating disease to treat. Even exhaustive laboratory tests may not be contributory to find out any underlying associations. Various modalities have been tried with varied outcomes. Injection botulinum toxin A (Btx A) has been used for the treatment of spastic, other motor conditions, and various types of neuropathies, notably trigeminal, postherpetic, and diabetic neuropathy.[2] So far, only three case reports of botulinum toxin usage in refractory erythromelalgia exist in the literature.[3-5]

A 42-year-old male presented with complaints of pain, increased warmth, and pin and needle sensation in both the hands for the past 3 years. The episodes were intermittent, aggravated on exercising or exposure to warm environments, and relieved on elevating or cooling the limbs. Physical examination revealed erythema, swelling, and raised temperature over the affected areas [Figure 1]. There were no features of primary and secondary Raynauds phenomenon. Nail-fold dermoscopy and neural examination were essentially normal. Pain on visual pain analog scale (VAS) was 8/10 (visual analog scale: 0–10, with 0 being no pain). The patient had tried various modalities of therapies in the past including aspirin, multiple NSAIDs, methylcobalamine, pregabalin, amitriptyline, gabapentin, carbamazepine, nifidepine, sildenafil, fluoxetine, citalopram, capsaicin topical gel, diclofenac gel, and various kinds of alternative balms with no satisfactory relief. A detailed diagnostic evaluation comprising assessment of baseline hematological parameters, biochemistry, C-reactive protein, ESR, thyroid profile, viral screen (HIV, HBsAg, Anti-HCV), VDRL, rheumatoid factor, antinuclear antibody, extractable nuclear antigen profile, antinutrophilic cytoplasmic antibody, complement levels, immunoglobulin levels, cryoglobulin, serum tumor markers, color Doppler of the limbs, ECG, X-ray chest, and cervical spine did not reveal any underlying systemic disease or associations. MRI cervical spine, CT scan thorax and abdomen, ultrasound abdomen, nerve conduction studies, and skin biopsy were essentially normal. The patient was finally clinically diagnosed as a case of erythromelalgia. One vial of botulinum toxin containing 100 unit was reconstituted by mixing 2.5 ml of normal saline. The reconstituted solution was withdrawn in an insulin syringe of 1 ml to make one marking of insulin syringe equal to 1 U of botulinum toxin. He was administered 1U of deep intradermal injection Btx A approximately 1 cm apart on the dorsal as well, palmar aspect covering all the fingers and mid potion of the palms and dorsum of hands with a total dosage of 50 U in each hand. The marking of botulinum toxin is illustrated in Figure 1. His pain subsided dramatically with VAS of 2/10 over 5 days. Gradually, he did not develop pain, redness, and swelling on the hands. Injection was repeated after an interval of 3 months and he was totally asymptomatic [Figure 2]. He is on regular 3-monthly follow-up. After three such sessions of intradermal botulinum toxin and a total follow-up of 06 months, he remains asymptomatic.

Presentation of (i) burning pain, (ii) erythema, (iii) raised temperature of the skin, and (iv) swelling of extremities getting precipitated by (v) heat, exercise, and physical dependency but relieved by (vi) elevation of limbs and cooling have long been proposed as clinical criteria by

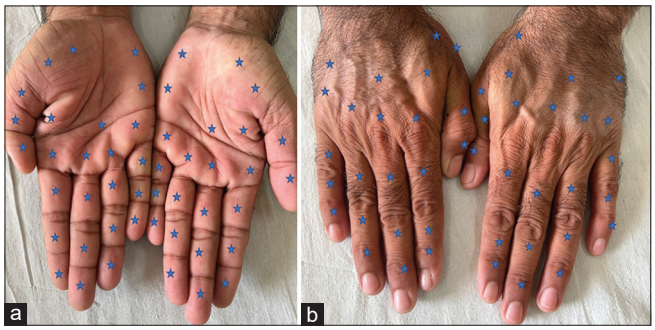

Figure 1: Illustrates the erythema and swelling of palm (a) and dorsal aspect of hands (b). Star marks show sites of botulinum toxin administration on the palms and dorsal aspect of hands

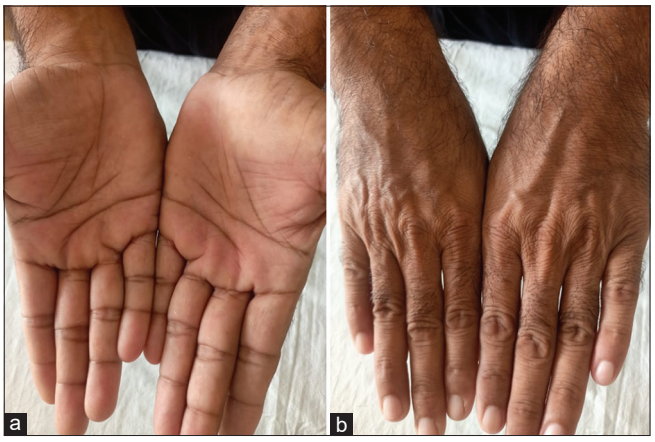

Figure 2: Illustrates the erythema and swelling of palm (a) and dorsal aspect of hands (b) have resolved completely

Thompson *et al.*[6] to diagnose the erythromelalgia. It has a profound impact on quality of life and can severely impact normal functioning of the individual to the extent the patient may seek for radical measures to alley the symptoms. Unlike secondary erythromelalgia, primary erythromelalgia has onset in the first decade of life with involvement of bilateral upper and lower extremities. The exact pathogenesis of this condition is obscure. However, it has been hypothesized that it is a disorder of vascular dynamics, wherein there is decreased capillary perfusion leading to tissue hypoxia along with increased cutaneous arteriovenous shunting which imparts erythematous, warm, and swollen appearance. Some authors consider Raynaud phenomenon and erythromelalgia as spectral conditions where one extreme is of vasoconstriction and the other is of reactive hyperemia, respectively.[7]

It requires exhaustive work-up to rule out associated hematological, metabolic, and musculoskeletal conditions, connective tissue disorders, infections, drugs, neuropathies, and malignancies, particularly in secondary erythromelalgia. Treatment of primary and secondary may differ due to its underlying causes and associations. There is great heterogenicity in the response from pharmacological agents. Aspirin, selective serotonin reuptake inhibitors (citalopram, fluoxetine), anticonvulsants (carbamazepine), calcium channel blockers (nifedipine) and tricyclic antidepressants (amitriptyline), nonselective sodium channel inhibitor (mexiletine), antianginal drug (ranolazine), topical capsaicin gel, diclofenac gel, lidocaine gel, infusions of nitroprusside, lidocaine, and prostaglandins, and more invasive procedures like sympathetic blocks, epidurals, and sympathectomy have been tried with varied response.[1]

The burning pain associated with erythromelalgia is essentially neuropathic pain, and the erythema and local heat are induced by intense neurogenic inflammation. We took clue from usage of Btx A in treating neuropathic pain. The plausible explanation of its efficacy in erythromelalgia can be explained by its role in inhibition of peripheral and central sensitization by blocking the release of proinflammatory neurotransmitters and pain mediators such as calcitonin gene-related peptide, substance P, and glutamate from nerve endings and dorsal root ganglion and by blocking the sodium channels in peripheral sensory neurons.[1] We conclude that botulinum toxin A might be an alternative drug in a case of refractory erythromelalgia; the higher cost is its limitation however; larger double-blinded controlled studies are required to establish its efficacy and follow-up period in true sense.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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