Case Report

Novel treatment modality in a case of resistant erythromelalgia

Vidya D. Kharkar, Agni K. Bose*, Pandharinath K. Khade

Department of Dermatology, King Edward Memorial Hospital and Seth GS Medical College, Mumbai, Maharashtra, India

Received: 07 September 2020
Accepted: 08 June 2020

*Correspondence:
Dr. Agni K. Bose.
E-mail: agnikumarbose@gmail.com

ABSTRACT

Erythromelalgia presents with redness, pain and warmth of the extremities, which is exacerbated by warming and relieved by cooling. Treatment of pain in erythromelalgia can be difficult, and often polypharmacy is utilized. No single therapy has been found to provide complete relief for any patient. Therefore, a multidisciplinary approach is required to treat pain and its significant negative impact across many domains of functioning. A 21 year old male diagnosed case of primary erythromelalgia since 5 years, presented multiple times with recurrent pain and erythema in bilateral lower limbs. Patient was treated initially with oral antibiotics, tramadol and prednisolone, without relief. Aspirin, amitriptyline, pregabalin, carbamazepine, atenolol were later added which gave him partial relief. Epidural caudal catheter with daily infusion of anesthesia was added along with topical buprenorphine patch when conservative polypharmacy failed to provide complete relief and later unilateral lumbar sympathectomy was done as a last resort. Adding pentoxifylline and compression therapy improved the patient’s condition drastically and complete remission is in progress. The patient required a multidisciplinary approach for pain management and surgical intervention was required due to his refractory nature. However, this also does not give complete relief and thus a combination of both medical and surgical methods is required for best control of symptoms.

Keywords: Erythromelalgia, Pentoxifylline, Sympathectomy, Resistant

INTRODUCTION

Erythromelalgia is a rare pain disorder characterized by burning pain, erythema and warmth, more frequently seen in the lower limbs, with an estimated incidence of 1.3 per 100,000 people.⁠¹⁷ These symptoms typically develop in patients when they are young, often in the first decade of their lives.⁠¹⁷ The symptoms are most typically acute and apparent during flares and are often aggravated during physical activity or exposure to heat. In spite of the prevalence of multiple treatment options, the condition is fairly difficult to treat, with limited instances of complete resolution.⁠²⁹

CASE REPORT

A 21 year old male, presented with a 5 year history of recurrent burning pain in bilateral lower limbs of moderate to severe intensity. He initially had burning sensation over soles which gradually spread till knees and this was followed by redness and swelling over both limbs. There was history of exacerbation after exposure to heat and relief after immersing his limbs in cold water and on elevating the limbs. The constant dipping in water, led to maceration of the skin and he later developed pustules which progressed to form multiple ulcers. His symptoms would be relieved during the winter months and exacerbate during summers and he had 4 episodes of hospitalizations for the same. On examination
there was diffuse erythema with scaling involving bilateral lower limbs. The legs were warm and tender on palpation. There were multiple well defined deep ulcers with punched out edges which later healed with atrophic scars. Fissures present over posterior aspect of bilateral legs and the web spaces showed maceration.

Figure 1: Diffuse bright erythema over bilateral lower extremities with multiple ulcerations.

Figure 2: Punched out ulcers over the shin.

Figure 3: Healed ulcers after 3 months of recombinant human epidermal growth factor gel.

Figure 4: After three weeks of pentoxifylline and compressive bandaging. Patient had decreased pain and erythema.

On routine investigations, his biochemical and hematological tests were within normal limits and myeloproliferative disorders and hypercoaguable states were ruled out. No abnormalities were detected within the Doppler and Nerve conduction studies. He was treated initially with a combination of pregabalin, tramadol, escitalopram, amitriptyline, carbamazepine, aspirin and atenolol for the burning pain which gave him partial relief. Oral and topical antibiotics as per culture sensitivity were added. However, the ulcers were still resistant to therapy and were not healing, thus recombinant human epidermal growth factor gel was added along with local wound care, and this led to complete healing of the ulcers with atrophic scars.

The patient was discharged on oral analgesics and he presented in the subsequent years during the summer months with exacerbation. Epidural caudal catheter with daily infusion of anesthesia (Bupivacaine 0.08%, Lignocaine 0.8%, Dexmedetomidine 25mcg) was added along with topical buprenorphine transdermal patch when conservative polypharmacy failed to provide complete relief. This led to a 75% reduction in the pain and burning sensation. Since the patient still didn’t have complete relief, reversible unilateral lumbar sympathetic block was initially tried, and when he tolerated it well, permanent unilateral lumbar sympathectomy was done. This led to reduction in the pain, but paradoxically increased the erythema. Thus we put him on pentoxifylline, topical capsaicin gel and tried compressive bandaging with roller gauze from his thighs to his legs. The patient’s condition has improved drastically with a 90% improvement in the pain and erythema after 3 weeks of this therapy.

DISCUSSION

Erythromelalgia is a rare condition characterized by intense burning pain, redness and warmth, most commonly seen in the bilateral lower extremities and is relieved by limb elevation and cooling by dipping the limbs in cold water. On doing a literature search, we could find approximately 329 case reports from across the world and only 3 cases reported from India as of May 2020. The disease can be either primary or secondary to haematological and myeloproliferative disorders. Primary erythromelalgia is an autosomal dominant disorder caused by mutations in the SCN9A gene encoding the Nav1.7 sodium channel in peripheral sensory neurons which lowers the pain threshold.

Vascular abnormalities also play a role in the pathophysiology of erythromelalgia. The precapillary sphincters are constricted while the arteriovenous shunts are open, creating an imbalance of increased total perfusion yet deficient nutritive perfusion. This results in coexistence of hypoxia and hyperemia in affected skin.

There is no universally effective treatment for erythromelalgia. The focus of therapy is support and
avoidance of trigger factors. Immediate relief can be sought by cooling or elevating the extremity to effectively attenuate or relieve symptoms. Patients should also be counseled about the use of safe cooling options such as fans and air conditioning. One must be careful using ice or immersing an extremity into an icy water bath to relieve symptoms, since this can lead to skin necrosis and ulceration. 

Ulcer management involves the basic principles of wound care and in those resistant to treatment; recombinant human epidermal growth factor gel appears to be a promising therapy.

Treatment of pain in erythromelalgia can be difficult, and often polypharmacy is utilized. Topical treatment includes capsaicin. Oral medication includes propranolol (10 mg 3 times daily), clonazepam, ciproheptadine, methysergide, piroxicam, pizotifen. Early reports suggested that aspirin promptly relieved erythromelalgia, but this appears true only for cases involving thrombocytopathy, polycythemia, or other blood dyscrasias. 

Other drugs include that inhibiting serotonin reuptake, such as venlafaxine and sertraline, paroxetine, fluoxetine, and tramadol. Tricyclic antidepressants such as amitriptyline can be used for pain reduction, but no remissions have occurred. Imipramine is also used. Anticonvulsants such as gabapentin (400-3600 mg/day) reduces erythromelalgia pain for many TEA members, but no remissions have occurred. 

Calcium antagonists such as nifedipine may also improve nutritional capillary flow. However, they have also been implicated in the onset of erythromelalgia. Misoprostol has also been suggested - doses up to 400 µg twice daily have been used, in contrast to a usual dose of 200 µg 4 times daily for nonsteroidal anti-inflammatory drug–treated gastropathies.

Parenteral approaches have included Nitroprusside infusions, which have been helpful in some children and adolescents. This may be the preferred treatment for severe erythromelalgia in these age groups. It is usually not effective in adults.

Invasive approaches have included sympathetic blocks and epidurals. There is support for doing sympathectomies if a diagnostic sympathectomy produces improvement. Lastly, control of intractable pain has been reported in one patient using dorsal column stimulator. 

Our case was unique since despite going ahead with the last line of treatment invasive sympathectomy, our patient still did not have complete relief of pain and instead had a paradoxical worsening of erythema and leg swelling. Since the pathology involves precapillary sphincter constriction leading to tissue hypoxia and increased blood flow through the arteriovenous shunts causing warmth and erythema, we tried pentoxifylline in our patient and this led to considerable pain relief due to improvement in the microvascular circulation. The use of compressive roller gauze also probably helps to reduce the warmth and erythema by redistributing the excess blood flow from the AV shunts to the tissue capillaries. There is a paucity of data regarding the use of pentoxifylline and compression therapy in erythromelalgia and thus this seems like a novel and economical treatment modality.

Thus we recommend the use of polypharmacy for adequate pain relief, recombinant human epidermal growth factor gel for difficult to treat ulcers and use of pentoxifylline and simple compression of the limbs to help alleviate the pain, warmth and erythema.

The ideal therapeutic approach remains to be defined. No single therapy has proved consistently effective, which supports the possibility that there are several subtypes of erythromelalgia. Although patients respond quite variably to medication therapy, careful trial and error often lead to substantial benefit.

**Funding:** No funding sources

**Conflict of interest:** None declared

**Ethical approval:** Not required

**REFERENCES**