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Primary Erythromelalgia Complicated by Cellulitis: A Case Report and Review of Literature

Sara Sharif, Lubaina Haider, Latoya Freeman, Isabel M. McFarlane*

Department of Internal Medicine, State University of New York, Downstate Health Sciences University, Brooklyn, NY 11203 USA
*Corresponding author: Isabel.McFarlane@downstate.edu

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Abstract Background: Erythromelalgia is a rare disease with increasing incidence. It manifests as episodic painful red extremities triggered by heat. External cooling provides temporary symptomatic relief but may lead to complications such as cellulitis. Management includes trigger control, behavioral therapy and pain management. Case Presentation: A 47-year-old African American male presented to the hospital with worsening bilateral lower extremity pain for three months. It was episodic, triggered by running and associated with erythema and swelling. Patient used cold water immersion and air conditioning for pain relief. One week prior to presentation, he developed painful blisters on his feet. On presentation, vital signs were stable, patient was afebrile. Acute infection was ruled out and he was discharged with outpatient rheumatology follow up for erythromelalgia. He returned one week later with worsening symptoms. CT scan of lower extremities indicated bilateral cellulitis. Patient was managed by medicine, dermatology, rheumatology, and podiatry for cellulitis, fungal infection, trench foot and primary erythromelalgia with antibiotics, antifungals, gabapentinoids and behavioral therapy. His infection resolved and pain improved. He was discharged with outpatient rheumatology follow up. Discussion: Erythromelalgia is a highly debilitating disease with episodes of burning erythematous extremities triggered by increase in skin temperature. Patients seek pain relief by excessive external cooling. Pathophysiology involves gain of function mutation in voltage gated sodium channels causing autoregulatory dysfunction of skin. Underlying disease mechanisms are ambiguous and may involve unidentified genetic components and unknown triggers. It is a clinical diagnosis. Therapy requires a multidisciplinary approach. Complications should be promptly addressed given attention next to symptomatic relief. There is a lack of disease specific treatment and complete remission is unlikely. Our patient responded well to gabapentinoids and behavioral therapy.

Keywords: *erythromelalgia, cellulitis, sodium-gated voltage channels, gain of function mutation, antibiotics*

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1. Introduction

Erythromelalgia means painful red limbs. It is a rare disease with increasing incidence [1]. It can be divided into Primary and Secondary EM. Despite vigorous research, disease pathophysiology is not clearly defined. It is presumed to involve skin vasculature and neuronal system secondary to gain of function mutations in voltage gated sodium channels [2]. Symptoms are triggered by increasing skin temperature. Consequently, the best approach to management is controlling triggers and cooling involved areas. However, patients often develop complications as a result of over-cooling. In the absence of treatment guidelines, various modes of pharmacological and surgical therapies are employed with variable results. Multidisciplinary approach involving behavioral therapy is proposed to be the most beneficial method [3]. In short, EM is an orphan disease warranting further research to keep pace with its increasing impact on our society.

2. Case Presentation

A 47-year-old African American male presented to the hospital for worsening bilateral lower extremity pain and blisters for 1 week. It started gradually, progressing to 7/10 intensity over the previous three months. It was episodic, triggered by heat, lasted from two to ten hours and relieved by external cooling. It radiated from his ankles to toes bilaterally and was associated with warmth, redness, and swelling. The patient had developed significant functional impairment including inability to run/walk long distances as these activities triggered his symptoms. He had been immersing his feet in cold water and cooling them in front of the air conditioning for 4-6 hours a day to alleviate his symptoms. One week prior to presentation, he had developed painful blisters on both feet expressing serous fluid. He denied fevers, chills, trauma, purulent discharge, bleeding, similar previous episodes or family history of a similar rash. His primary

care physician prescribed gabapentin which did not relieve his symptoms. The patient had no complaints of the upper extremities or digits. On presentation, vital signs were stable, patient was afebrile. The physical examination was unremarkable except for edema, erythema, and tenderness to palpation on light touch on both feet and ankle. No motor and sensory changes were noticed. Pulses were palpable bilaterally. Figure 1.

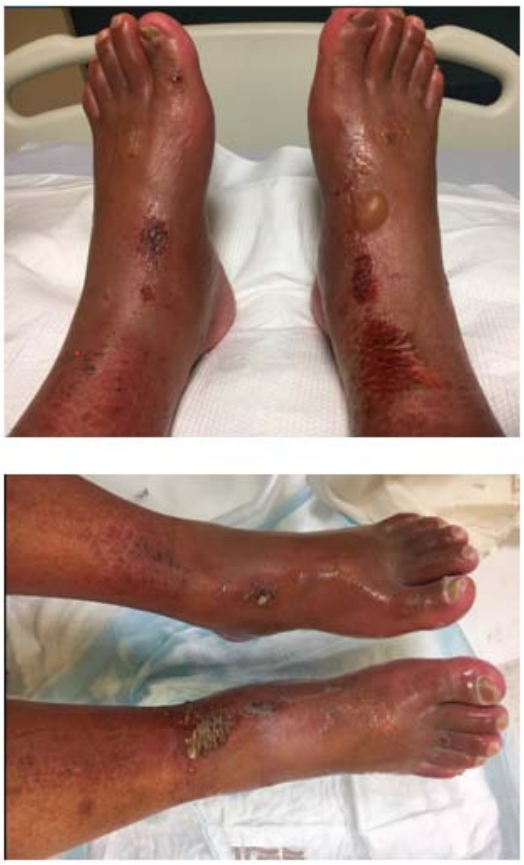

Figure 1. Appearance of the patient's bilateral lower extremities demonstrating erythema, edema, macerated scales, blisters and pitted keratolysis

Differential diagnosis included acute infection i.e. cellulitis secondary to repeated cold water immersions and dry air cooling as well as secondary erythromelalgia from autoimmune disorders, sexually transmitted infections and myeloproliferative syndromes. Consequently, Rheumatology service was consulted, and recommended work-up for secondary causes of EM. Vascular surgery evaluation found no need for urgent intervention as acute infection and peripheral vascular disease seemed unlikely.

Based on the clinical picture, hemodynamics and unremarkable lab results, acute infection was ruled out. His chronic symptoms required outpatient follow up with rheumatology for long term management of erythromelalgia. He was advised to continue pain management as prescribed by his PCP until his follow up rheumatology appointment to discuss his lab results.

However, the patient returned to the ED one week after with worsening symptoms. His vital signs were stable, physical exam showed that moderate erythema progressed from bilateral feet up to the lower third of anterior shins, edema with multiple scattered blisters in different stages of healing along with macerated scales, and pitted keratolysis on bilateral plantar surfaces. He had intact sensation and complained of tenderness to palpation.

Table 1. Laboratory Data

Serum	First admission	Second admission	Reference Range
WBC (K/uL)	7.10	9.33	4.5-10.9
RBC (M/uL)	4.60	4.62	4.2-5.4
Hemoglobin (g/dL)	13.4	13.7	12.0-16.0
MCV	85.9	89.0	78.0-95.0
Hematocrit (%)	39.5	41.1	37.0-47.0
Platelets (K/uL)	368	352	130-400
Sodium (mmol/L)	147	140	136-146
Potassium (mmol/L)	4.6	4.5	3.5-5.0
Chloride (mmol/L)	106	96	98-106
CO2 (mmol/L)	22	27	24-30
BUN (mg/dL)	14	11	6-20
Creatinine (mg/dL)	1.13	1.06	0.4-1.2
Calcium (mg/dL)	10.29	10.0	8.4-10.3
Total Protein (g/dL)	7.3	7.7	6.0-8.5
Albumin (g/dL)	4.6	4.6	2.8-5.7
AST (U/L)	20	23	10-35
ALT (U/L)	24	24	0-31
Alk. Phos (U/L)	87	124	25-125
Total Bilirubin	0.37	0.31	0.0-1.2
Glucose (mg/dL)	129	134	70-99
Hb A1C	5.2		
ESR(mm/h)	15	38	0-20
CRP(mg/dL)	0.74	12.72	1.0-4.0
TSH (miU/L)	1.77		0.27-4.20
Vitamin B12 (pg/mL)	798.8		211-946
Lactate (mmol/L)		3.6	0.5-2.2
HIV test		Negative	Negative
Chlamydia	Negative		
N. gonorrhea	Negative		
Urine Analysis			
Color	yellow		Yellow
Clarity	Clear		Clear
pH	6.0		<8.0
Spec Gravity	1.011		1.005 – 1.030
Protein	Negative		Negative
Glucose	Negative		
Ketones	Negative		
Hemoglobin	Negative		
Bilirubin	Negative		
Urobilinogen	0.2		0.2 – 2.0
Nitrite	Negative		Negative
Leukocyte Esterase	Negative		Negative
Immunological work-up			
C3 level	125		86-184
C4 level	34		20-58
Antinuclear antibodies	1:40		<1:40
ds-DNA (IU/ml)	54		<100
Anti-SSA	Negative		Negative
Anti-SSB	Negative		Negative
B-2 macroglobulin	2		Negative
Anti-cardiolipin IgG	9.4		0.0 – 12.5
Anti-cardiolipin IgM	<5		0.0 - 12.5
Anti-cardiolipin IgA	<5		0.0 – 12.5
Lupus anticoagulant	Positive		
Anti RPN	Negative		
Anti-centromere	Negative		@ 1:40
Anti Scl-70	Negative		
Anti-parietal cell	<1:20		<1:20
p-ANCA	9		<100
c-ANCA	15		<100
Protein Electrophoresis			
Alpha-1 globulin	0.3		0.1 – 0.4
Alpha-2 globulin	0.7		0.5 1.0
Beta globulin	0.8		0.5 1.0
Gamma globulin	1.0		0.6 – 1.6
Protein, total	6.3		6.0 – 8.3
Wound Culture		No growth	No growth

Repeat labs were unremarkable except for an elevated CRP. The rheumatological work up sent out on previous admission showed weakly positive ANA titer at 1:40 and a positive lupus anticoagulant.

Given the cellulitis-like picture of the lower extremities, he was admitted and started on IV vancomycin. Dermatology was consulted for further recommendations. Imaging was ordered for confirmation of the diagnosis. Figure 2 A, B and Figure 3.

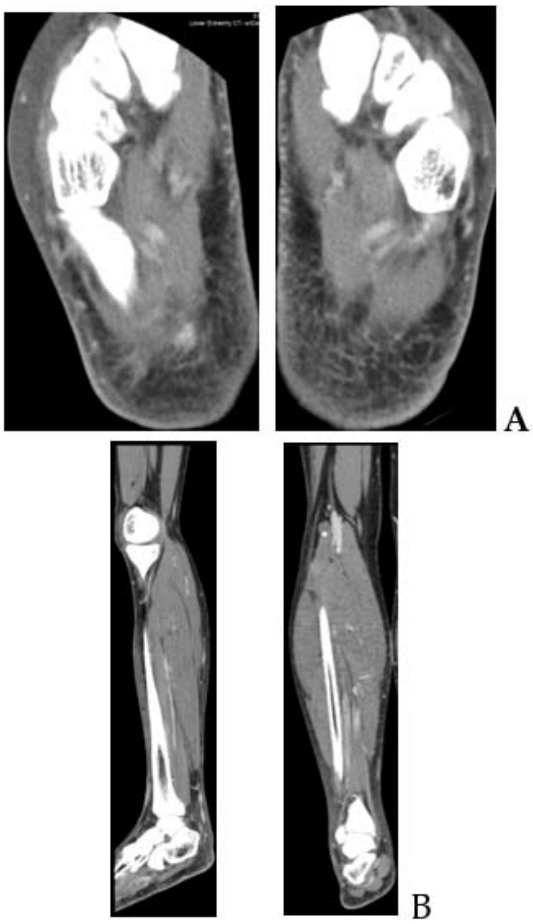

Figure 2 A, B. Contrast enhanced CT scan of the bilateral lower extremities demonstrated bilateral cellulitis without evidence of fluid collection or abscess

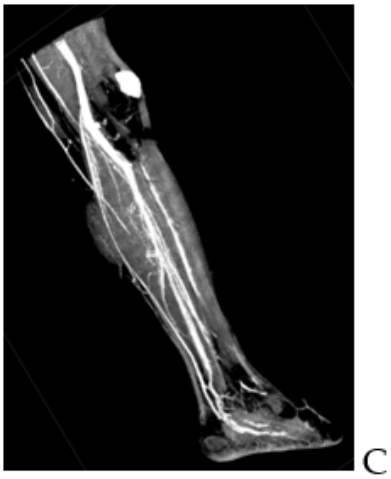

Figure 3. The vascular system of the lower extremities as shown in the 3D MIP is patent. The lower extremity Doppler was also negative for deep vein thrombosis

The patient was managed by a multidisciplinary team composed by medicine, dermatology, rheumatology, and podiatry. Based on the clinical findings, rheumatological lab results and imaging, the patient was diagnosed with primary erythromelalgia with secondary bacterial (cellulitis) and fungal (tinea pedis) superinfection and trench foot from prolonged cold-water immersions. Protein electrophoresis was also done to rule out myeloproliferative disorders.

After 3 days of IV vancomycin therapy, he was transitioned to trimethoprim-sulfamethoxazole DS for 7 days. He was also given Azole anti-fungal cream for topical application to his lesions. His wounds were regularly cleaned and dressed. For his EM, he was started on gabapentin 200 TID, pregabalin 75 mg BID and lidocaine patch. Tylenol was added PRN and daily Aspirin 325 was started. Intermittent ice packs were applied for symptomatic relief and he was advised to stop cold water immersions.

During his hospitalization, he showed mild improvement in pain but still complained of ambulation triggering his symptoms. His cellulitis resolved and wound cultures prior to discharge showed no bacterial growth. Symptomatically, his pain level dropped to 2/10, lasting 2 hours and improving with ice packs. After 4 days of hospitalization, he was discharged with a course of antibiotics, aspirin, pregabalin, and lidocaine patch. He was given follow up appointment for the rheumatology clinic for long term management of EM. He was also educated about a specialized erythromelalgia center in the city as genetic testing for the disease was not available at our institution.

3. Discussion

Erythromelalgia is a disease with increasing incidence but limited knowledge. In Minnesota, its incidence was 1.3/1000000, increasing each decade from 1978 to 2008, with female preponderance and median age of diagnosis of 61 years [1]. Small epidemiological studies in USA, Sweden and Norway provide poor estimates of the current prevalence of EM. [1,4]. In 2019, 14 EM cases have been reported in the literature despite the high probability of missed diagnosis and non-reported cases [5-17].

EM dates back to 1960s, being described as painful red limbs [18]. Overtime it has evolved into a separate disease entity with primary and secondary forms. EM associated with systemic diseases such as myeloproliferative disorders (polycythemia vera, idiopathic thrombocytopenia, leukemia, cryoglobulinemia, systemic mastocytosis), autoimmune diseases (lupus erythematosus, rheumatoid arthritis, mixed connective tissue disease, Sjogren's syndrome), infections, neoplasms, neurologic diseases (reflex sympathetic dystrophy, small fiber neuropathies, neurofibromatosis, multiple sclerosis/MS), pregnancy, drug exposures and alcohol abuse is termed as 'secondary' erythromelalgia [2,7,19].

"Primary" erythromelalgia occurs in the absence of its known associations. Patients may have co-morbidities such as hypertension, atrial fibrillation, diabetes, Raynaud's phenomenon, peripheral neuropathy, low back pain, hypothyroidism, bullous pemphigoid, gastroesophageal

reflux disease, chronic constipation, C. difficile infection, joint hypermobility syndrome and even hyper Osmia [5,9-12,16,19-21].

To date, there is no classification criteria for EM diagnosis given the lack of consensus in regard to clinical presentation and associated comorbid conditions.

Our patient was diagnosed with primary EM after an exhaustive work-up ruled out secondary causes of disease.

Erythromelalgia has been considered to result from hypoxic tissue injury secondary to reduced perfusion of distal extremities. Irregular vasodilation can lead to an increased shunting of blood through the arterio-venous (AV) anastomosis, causing ischemic damage with release of inflammatory mediators manifested as hyperemia, pain and inflammation of the involved area [2,3]. EM patients have reduced capillary size & density in areas of increased AV anastomosis [11]. Eighty-eight percent of EM patients had dysautonomia with abnormal thermoregulatory skin tests [22]. This 'vascular hypothesis' is also supported by the high risk of myeloproliferative (MPO) disorders observed among EM patients.

In the year 2000, Davis et al. reported that 63% of EM patients had small fiber neuropathy, but it was not until 2004 that a mutant voltage-gated sodium channel (VGSC) 'Nav 1.7' encoded by SCN9 gene was discovered [23,24]. Since then, research has targeted the relationship between pain perception and VGSCs in sensory neurons, especially Nav1.7, Nav1.8 and Nav1.9 encoded by SCN9, SCN10 and SCN 11 genes respectively [24,25,26]. In a systemic review of pediatric population, 15 different SCN9A gene variants were found in 25 children with EM [25]. Patients with variant SCN9 mutant VGSC showed increased pain perception at higher temperatures and experienced EM-like symptoms more frequently compared to non-variant SCN9 and SCN10 mutant forms [26].

Nav1.7 channels are expressed predominantly in the dorsal root ganglion and nociceptive fibers [2]. In 2015, Frank et al. discovered Nav1.7 channel in tunica media myocytes and tunica intima endothelium of skin arterioles and AV shunts as well as in small fiber sensory and sympathetic neurons innervating them. [27] Nociceptive fibers carrying these channels release inflammatory mediators e.g. substance P when stimulated [2,27]. This study links the vascular and neuronal hypothesis of EM, gain of function mutations of VGSC being central to both. It has been postulated that at higher temperatures, mutant VGSC in sensory neurons, sympathetic neurons and skin vasculature simultaneously discharge impulses at high frequency leading to pain hypersensitivity with release of inflammatory mediators, dysautonomia and vasodilation. Thus, shunting blood away from the capillary beds, inducing hypoxia and inflammation at the site [2,22,28,29].

It is very likely that the role of SCN9 family of genes is only cumulative to a yet unidentified constellation of mutations [10,13], necessitating further research in exploring mutations unique to the skin vasculature. Given unexplained risk of development of MPO secondary to EM, we should also consider JAK2 mutations in primary disease pathophysiology. Also, there is little research evaluating erythromelalgia as an autoimmune disorder given its association with autoimmune diseases [2,3].

There is a lack of standardized testing for EM, so diagnosis is made clinically & by exclusion. Complete blood counts and liver function tests are done for ruling out MPO disorders, ANA, CRP, ESR, anti Ro, anti La, anti SMA, anti-centromere antibodies for autoimmunity and nerve testing (nerve conduction studies, electromyography, autonomic reflex screen e.g. quantitative sudomotor axon reflex test) for neuropathies. The serological studies were negative in our patient as mentioned above.

Physicians use various methods for disease evaluation. Thermoregulatory sweat testing for abnormal thermoregulatory function [22], late blood restoration test (LBRT) to distinguish vasoparalysis in EM from a vasoconstrictive disorder, laser speckled contrast imaging (LSCI) to monitor capillary blood flow [11], capillaroscopy to visualize skin capillary changes [29,30] and thermography to compare acute attacks with asymptomatic periods [6]. Even bone scan documented non-specific findings, opening avenues for radiological testing in future [31]. Widely applied skin biopsy relays information about disease complications but is not diagnostic. We chose not employ imaging techniques and biopsy in diagnosing our patient due to unknown efficacy of these tools as diagnostic studies.

To eliminate the subjectivity of pain, various pain scales e.g. visual analogue scale, neuropathic pain scale, small fiber neuropathy-symptom inventory questionnaire SFN-SIQ have been used to calibrate symptom severity and response to treatment [26]. Researchers found that the difference in pain reported by different individuals of the same family corresponded with the difference in in-vitro neuronal excitability of induced pluripotent stem cells from these individuals [32]. Genetic testing has been used to confirm the diagnosis of the disease. However, these methods are uncommon, expensive and require specialized centers.

Signs and symptoms of erythromelalgia are intermittent, lasting hours to days based on individual variability. Most commonly involved areas include distal extremities, but involvement of face, ears and cheeks is also seen [2,12,14]. Symmetrical bilateral involvement is more common than asymmetrical unilateral symptoms. As per review article from 2018, >80% of the lower limbs and >25% of the upper limbs are affected which also corresponds 9/14 cases with lower extremity and only 1 case with isolated upper extremity involvement in 2019 [2]. In our patient, there was bilateral lower extremity involvement.

As described above, an acute attack is burning pain in the extremities but sensations like pins and needles, electric shock, throbbing and intense itching are also seen [2,3]. Whether this spectrum of symptoms corresponds to disease severity and prognosis is unknown but may encourage a new symptomatology-based classification scheme of the disease.

Most cases of primary EM are triggered by increased skin temperature, internally by increased metabolism (running, jogging) or externally by environmental temperature (summers, humid work atmosphere) [2,3]. The inability to thermoregulate coupled with increased pain sensitivity leads to characteristic burning pain [22,28]. The triggers identified by patients are confirmed during disease workup. It is unknown whether triggers are the cause of initial insult or a consequence of it. An EM epidemic during summer in China suggests that a large

part of asymptomatic population may carry silent mutations increasing their susceptibility to triggers [33]. Now, global warming threatens a worldwide epidemic unless the extent of involvement of heat triggers is proactively explored.

Just like in our patient, EM victims are caught up in a vicious cycle of cooling affected areas, damaging skin and causing pain aggravation. They use fans, cold water immersion, open shoes, reduced exercise and ice on affected areas [2,3]. Prolonged exposure causes skin maceration, infections (cellulitis), frost bite and hypothermia [2,3,6,15,17]. It causes depression, anxiety and suicidal ideation in patients [6]. A patient reportedly chose an elective surgical procedure for pain relief, despite improvement on medical treatment which reflects their frustration [16].

Due to disease rarity and lack of standard testing, new disease onset often goes unrecognized making it difficult to monitor disease free intervals, number and nature of EM attacks. Davis et al. estimated mean 1.38 episodes of erythromelalgia/week in 168 patients with no comment on the symptom free interval [34]. Given increasing incidence of EM, there is a need to update this data through further research.

Trigger control is the most important aspect of disease management. Patients are advised to keep their extremities cool, avoid closed shoes and prolonged exercise, use saline foot immersion and limit excessive cooling [2,3]. Behavioral therapy can revert suicidal ideation and return patients to a functional status [6]. In case of development of complications such as cellulitis, infections must be treated first followed by pain management [15]. Treating these patients is a clinical dilemma as excess cooling causes life threatening hypothermia [17]. Psychiatrists should be readily involved to motivate depressed patients. A multidisciplinary approach is the best way to achieve good outcomes. For this reason, we consulted rheumatology, vascular surgery, dermatology, infectious disease and podiatry to devise optimal management plan for our patient. Moreover, education was provided regarding lifestyle modifications and cooling mechanisms to help him cope with his disease.

Initially, the mainstay of pharmacological therapy used to be aimed at maintaining adequate perfusion to affected area with antiplatelets such as aspirin and prostaglandins. Calcium channels blockers and serotonin and norepinephrine reuptake inhibitors (SNRIs) are believed to relieve tissue hypoxia through vasodilation. SNRIs also decrease sympathetic nerves firing by blocking norepinephrine uptake which improves thermoregulation. Like any inflammatory pain, almost all patients have had a trial of non-steroidal anti-inflammatory drugs (NSAIDs), but it is rarely successful [2].

Discovery of mutant sodium channels was a game changer as patients showed improvement with partial sodium channel blockers e.g. mexiletine and lidocaine combined with other modalities of pain treatment [3,14]. Topical formulations like amitriptyline-ketamine, lidocaine, capsaicin, midodrine and neuronal calcium channels modulators like gabapentin have also been used [3,12]. Decreased pain perception through targeted Nav1.7 channel antagonism is still experimental whereas mutant potassium channels antagonism and NAD synthesizing mutant NMNAT2 enzyme potentiation is yet unexplored [13,32,35]. So far, we have been unable to market an effective and safe EM specific pharmacologic therapy.

Despite association of EM with autoimmune disorders, a small study with 17/36 steroid responsive patients was insufficient for approval of immunosuppressants as first line agents [36]. Similarly, there was no instance of opioid induced disease remission of 292 cases reviewed by Tham et al [17]. Sodium nitroprusside, beta blockers and nicotinic acid used in isolated cases are far from being mainstream drugs for EM. [2]

Surgical intervention such as epidural sympathetic blockage and peripheral nerve blocks has been used for refractory pain. Both, popliteal nerve perineural catheter and ropivacaine/fentanyl infusion, induced remission after failure of opioids neuroleptics and NSAIDs. A teenager responded to L3-4 ropivacaine infusion after failure of peripheral nerve block. Botulinum toxin injected in involved areas achieved opioid independence by inhibiting the release of substance P and glutamate [8].

Our patient responded well to gabapentinoids and topical lidocaine patches. Given high risk of MPO, we also started him on daily aspirin which was well tolerated. However, given increased bleeding risk with concomitant use of aspirin and NSAIDs, the latter were not prescribed. Surgical intervention was not considered due to good response to pharmacological therapy. Moreover, since there has been no study comparing the efficacy of these invasive procedures, we are unable to place one modality of treatment over another, emphasizing the need for step by step guidelines for treatment of EM.

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