PAIN MEDICINE
Volume 7 • Number 6 • 2006

CASE REPORT

Erythromelalgia: A Case Report and Literature Review

Charles J. Buttaci, DO, PT

Department of Physical Medicine and Rehabilitation, University of Medicine and Dentistry of New Jersey-New Jersey Medical School, Newark, New Jersey, USA

ABSTRACT

Objective. Erythromelalgia is a rare condition, of uncertain etiology, characterized by episodic erythema, intense burning pain and warmth of the hands and/or feet, and when chronic, associated with significant disability. The diagnosis is based on a thorough history and physical exam during a painful episode along with diagnostic testing to exclude other causes. This paper describes the unique syndrome of erythromelalgia through a case report and literature review.

Design. Case presentation and literature review.

Patients. A 44-year-old male with erythromelalgia.

Conclusions. Despite multiple treatment options, erythromelalgia is a challenging disease to effectively manage. Early recognition and treatment, may offer patients the best probability of achieving remission or significant improvement.

Key Words. Erythromelalgia; Pain; Neuropathy; Vasculopathy

Case Report

A 44-year-old right-handed man without any significant past medical history presented with a 1-year history of episodic bilateral burning pain in his hands. He reported an associated warmth and erythema in all fingers exacerbated by activity and rarely occurred at rest. He noticed mild improvement with ibuprofen 600 mg and cessation of activity. At the time of the initial examination the patient reported that he was asymptomatic and thought that his condition may be improving. Visual inspection revealed no obvious erythema and palpation failed to reveal any tenderness or signs of synovitis. A thorough neurological examination was normal. Carpal compression test was equivocal on the right and negative on the left. Phalen's and Tinnel's at the wrist were negative. Cervical spine motion was normal and Spurling's test was also negative for radiating symptoms. A recent upper extremity electromyography completed by another physician was normal. Bilateral X-rays of the hands and wrists, cervical spine and brain magnetic resonance imaging were all normal and there was no significant abnormality detected on a triple phase bone. His erythrocyte sedimentation rate was 3 and an antinuclear antibody and a Parvovirus antibody were also negative. The patient was advised to complete a pain journal and obtain the remainder of his medical records from previous physicians. Given his relief with ibuprofen, samples of celecoxib 200 mg daily were provided

The patient was re-evaluated 4 weeks later. Immediately prior to this evaluation, the patient spent several hours building a bookcase as part of his carpentry hobby and reported significant pain in his feet, in addition to his hands. At this

Reprint requests to: Charles J. Buttaci, DO, PT, Department of Physical Medicine and Rehabilitation, University of Medicine and Dentistry of New Jersey-New Jersey Medical School, 30 Bergen Street, ADMC 1, Room 101, Newark, NJ 07101-1709, USA. Tel: 973-972-3606; Fax: 973-972-2825; E-mail: chuckbuttaci@yahoo.com.

 1526-2375/06/$15.00/534 534–538

time, there was significant erythema and warmth present involving both regions. He reported that since the last visit, he noticed marked relief with elevation or cooling of the limbs in cold water. He denied any significant relief with celecoxib. Review of his medical records indicated that previous unsuccessful treatments included rofecoxib 25 mg daily for 2 months, a methlyprednisolone dose pack, and gabapentin 900 mg tid. Prior to the follow-up evaluation, a thorough literature review was completed. Given his history, clinical examination findings, and a lack of any obvious pathology on diagnostic testing, a diagnosis of erythromelalgia was provided. It was explained that current treatment options include activity modification, gabapentin, calcium channel antagonists, tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), and invasive procedures. He deferred pharmacological intervention and expressed an interest in activity modification. The patient was advised to avoid any strenuous activity in a warm environment. When he first noticed the onset of his symptoms he was instructed to abruptly discontinued the precipitating activity and cool his hands in cold water. He was advised to have an annual hematology evaluation including a complete blood count (CBC) with differential given the association of myeloproliferative disorders with the secondary form of the syndrome. A telephone conversation a few months later revealed that his symptoms were present with certain activities but manageable at rest.

Approximately 1 year later, he reported that his symptoms still occurred with prolonged UE activity. However, he is more aware of the typical onset of symptoms and immediately lessens his activity while completing the majority of his physically demanding tasks in a cooler environment, in the basement or outdoors on cold days. There was no report of any myeloproliferative disorders detected on CBC completed by his internist. In summary, it appears that the patient developed a case of primary erythromelalgia, which responded reasonably well to activity modification. If he was interested, a thorough trial of medications may have provided additional relief.

Clinical Presentation and Associated Disorders

Many patients will present similar to the patient in the case study with a complaint of insidious intermittent intense symmetrical bilateral burning pain in the hands and feet, which may radiate proximally. The age of onset varies significantly. The primary form may begin spontaneously at any age, while the secondary form typically occurs in association with myeloproliferative diseases, neuropathies, and autoimmune diseases [1,2]. The pain will often fluctuate in intensity and duration with symptoms typically appearing late in the day [1]. Symptoms are often provoked by elevated temperatures, either ambient or exercise induced. Alleviation is often achieved from elevation and cooling the involved limbs. Further description of the clinical presentation of erythromelalgia has been well documented by Davis et al. [3].

Very often the diagnosis will be made exclusively on details provided in a thorough history, as patients are frequently without physical examination findings during asymptomatic intervals. Kalgaard et al. described the criteria for fulfilling the diagnosis of erythromelalgia as burning pain in the hands and/or feet associated with increased temperature and erythema, with symptoms relieved by cooling and aggravated by warmth [2]. If a patient presents while experiencing symptoms the findings are rather obvious. If the patient is asymptomatic, some authors recommend immersing an affected region in hot water for up to 30 minutes [1]. Another reasonable alternative involves the patient taking a photograph or videotaping the affected region during an episode.

Unfortunately, there is no diagnostic test to clearly confirm the diagnosis. However, diagnostic imaging and laboratory evaluation are often necessary to exclude other entities in the differential diagnosis and exclude more concerning secondary etiologies. As there is a relatively well-documented association between erythromelalgia and myeloproliferative disorders, a CBC with a differential count is recommended [2,4]. Several authors have reported the onset of symptoms may precede detectable myeloproliferative diseases by several years. If the initial CBC is within normal limits, the patient should be advised on the benefit of routine follow-up evaluation. Multiple immunology markers including rheumatoid factor, antinuclear antigen, antineutrophil cytoplasmic antibodies will be normal unless another disease process is present [2].

Since Babb et al. reported the increased incidence of myeloproliferative diseases associated with the disorder in 1964, many other comorbidities have been documented [3,5]. Cohen summarized the most extensive collection of disorders that have been associated with erythromelalgia [1]. This list includes hematological disorders includ-

Table 1 Historical reports and theories pertaining to erythromelalgia

Author(s)	Year	Theories and Observations	Evidence
Graves [7]	1843	N/A	N/A
Mitchell* [8]	1878	Vasomotor neurosis	Clinical observation
Lewis [9]	1933	Excessive response of pain substance within the skin	N/A
Mufson [10]	1937	Vascular distention due to hydrostatic pressures	Clinical observation
Uno and Parker [11]	1983	Lack of sympathetic activity producing vasodilation	Clinical observation
Kvernebo [12]	1998	Vascular impairments with precapillary sphincter constriction and dilated anastomotic shunts	Laser Doppler perfusion imaging and skin temperature measurements at rest and with symptoms in 14 patients with erythromelalgia
Littleford et al. [13]	1999	Subclinical vasoconstriction and reactive hyperemia	Skin temperature measurements
Cohen [1]	2000	Hyperemia mediated pain	Clinical observation
Davis et al. [3]	2003	Small fiber neuropathy and vasculopathy	Autonomic reflex screening, NCS/EMG, Doppler, Oximetry in 67 patients with erythromelalgia

* Credited with coining the term "erythromelalgia."
N/A = not applicable; NCS = nerve conduction study; EMG = electromyography.

ing polycythemia, thrombocythemia, myeloid leukemia, pernicious anemia, and thrombotic thrombocytopenic purpura. Connective tissue disorders include rheumatoid arthritis, systemic lupus erythematosus, Sjogren's syndrome, and vasculitis. Neuropathies, multiple sclerosis, and spinal cord disease are among the neurological disorders that have been associated with erythromelalgia. Malignant causes include carcinoma of the colon and thyroid and astrocytomas.

Pathophysiology and Proposed Theories

Although primary and secondary forms of the disorder have been reported for over 100 years, the precise etiology and optimum management remain elusive [6–10]. Many theories to explain the disorder have been postulated over the years as noted in Table 1. Although the exact pathological mechanisms responsible for the clinical presentation are still being disputed, it appears that vascular shunting and reactive hyperemia are at least partially responsible for the clinical presentation.

Treatment Options and Prognosis

Many treatment options have been introduced over the years, all with significant variations in response. As noted in Table 2, documented treatments include the more commonly used oral neuropathic medications, intravenous (IV) infusions, and invasive procedures such as sympathectomies and dorsal column stimulators [1,3]. There is no universal treatment that relives the discomfort in all patients. Current opinion suggests educating the patient on activity modification and if necessary initiating treatment with oral medications

Table 2 Treatment approaches with reported success in managing erythromelalgia

Author(s)	Treatment	Potential Adverse Reactions
Several	Avoiding strenuous exercise and warm environments	Compromise in activities of daily living
Several	Elevating and applying ice to involved extremity or soaking in cold water	Frostbite, "immersion foot"—maceration of skin, ulcerations
Muhiddin et al. [14]	Capsaicin cream bid	Local irritation
Cohen [1]	Magnesium	Flushing, muscle weakness, hypotension
Herkovitz et al. [15]	TCAs: amitriptyline	Arrhythmias, seizures, hypotension, drowsiness
Rudikoff and Jaffe [16]	SSRIs: paroxetine, sertaline	Gastrointestinal complaints, tremor, male sexual dysfunction
McGraw and Kosek [4]	Gabapentin	Somnolence, ataxia, dizziness, eight gain
Belch [17]	Nifedipine-extended release	Dizziness, headache, hypotension
Several	Beta blockers: propanolol, labetalol	Bradycardia, hypotension
Mork et al. [18]	Misoprostal 400 μg bid	Diarrhea, abdominal pain
Levine and Gustafson [6]	Aspirin	Bleeding, peptic ulcers
Stone et al. [19]	IV nitroprusside	Hypotension, drowsiness, confusion
Kuhnert et al. [20]	IV lidocaine	Arrhythmias, seizures, respiratory arrest
Sano et al. [21]	IV cyclosporinee	Seizures, leukopenia, hepatotoxicity, malignancy
Rauck et al. [22]	blocks, sympathectomies, dorsal column stimulators	Epidural analgesic infusions, sympathetic Procedure specific

with relatively benign adverse reactions: gabapentin, SSRIs, TCAs, and calcium channel antagonists. Quite often a combination of modalities may be required to provide effective management. IV medications and invasive procedures are typically reserved for refractory cases and extremely painful debilitating episodes. It is difficult to predict which patients will achieve any significant improvement or remission with a specific treatment.

Much of the information pertaining to disease prognosis, associated comorbidities and disability is derived from a study conducted by Davis et al. at the Mayo Clinic. This was a retrospective medical record review of 168 patients with follow-up by means of a survey questionnaire. The results indicate that 31.9% reported their symptoms worsened since their initial Mayo Clinic visit, 26.6% were about the same, 30.9% decreased, and 10.6 completely disappeared [23]. The average rate of episodes was 1.38 per week. Local complications including skin damage due to cold water or ice were reported among 21.8% with 1.1% suffering gangrene [23]. Perhaps most concerning was the functional impairments that developed. Fifty percent of the population admitted to an inability to walk long distances, with 12.5% having to give up a job and an equal number unable to drive any longer [23]. Also of interest was the reported comorbidities with 8.9% of the study population having a form of myeloproliferative disease: polycythemia vera in nine patients, essential thrombocythemia in four, and chronic granulocytic leukemia in two [23]. The causes of death included common medical conditions such as cardiovascular, cerebrovascular, pulmonary, and solid cancers. Myeloproliferative disease accounted for six deaths. The authors concluded by stating that no single medication or method of treatment was found to be universally helpful, with 84 different medications and therapeutic methods attempted by the study population.

In conclusion, erythromelalgia is a rare condition characterized by episodic burning pain, erythema, and warmth in the hands and/or feet likely mediated by arterial venous shunting and/or reactive hyperemia. The diagnosis is based on history and physical examination during a painful episode. Initial treatment consists of activity modification and a trial of oral analgesic medications, as no treatment is consistently effective. Patients and referring physicians should be advised on periodic screening for hematological disorders, given the association of these entities with secondary erythromelalgia. Classification of the disorder may help in providing a prognosis. Further research to better appreciate the precise pathophysiology and guide effective treatment is warranted.

References

1 Cohen JS. Erythromelalgia: New theories and new therapies. J Am Acad Dermatol 2000;43:841–7.
2 Kalgaard OM, Seem E, Kvernebo K. Erythromelalgia: A clinical study of 87 cases. J Intern Med 1997;242(3):191–7.
3 Davis MP, Rooke T. Erythromelalgia. Cardiovasc Med 2002;4:207–22.
4 McGraw T, Kosek P. Erythromelalgia pain managed with gabapentin. J Anesthesiol 1997;86(4): 988–90.
5 Babb RR, Alarcon-Segovia D, Fairbairn JF. Erythermalgia: A review of 51 cases. Circulation 1964;29:136–41.
6 Levine AM, Gustafson PR. Erythromelalgia: Case report and literature review. Arch Phys Med Rehabil 1987;68:119–21.
7 Graves RJ. A System of Clinical Medicine. Dublin: Fannin; 1843. Third American edition with notes etc by William Gerhard, Philadelphia, 1848.
8 Mitchell SW. On a rare vaso-motor neurosis of extremities and on maladies with which it may be confounded. Am J Med Sci 1878;76:17–36.
9 Lewis T. Clinical observations and experiments relating to burning pain in the extremities, and to so-called 'erythromelalgia' in particular. Clin Sci 1933;1:175–211.
10 Mufson I. Clinical observations in erythromelalgia and method for its symptomatic relief. Am Heart J 1937;13:483–91.
11 Uno H, Parker F. Autonomic innervation of the skin in primary erythromelalgia. Arch Dermatol 1983;119:65–71.
12 Kvernebo K. Erythromelalgia: A condition caused by microvascular arteriovenous shunting. Vasa 1998;(suppl 51):1–40.
13 Littleford RC, Khan F, Belch JJ. Skin perfusion in patients with erythromelalgia. Eur J Clin Invest 1999;29:588–93.
14 Muhiddin KA, Gallen IW, Harries S, Pearce VR. The use of capsaicin cream in a case of erythromelalgia. Postgrad Med J 1994;70:841–3.
15 Herkovitz S, Loh F, Berger AR, Kucherov M. Erythromelalgia: Association with hereditary sensory neuropathy and response to amitriptyline. Neurology 1993;43:621.
16 Rudikoff D, Jaffe IA. Erythromelalgia: Response to serotonin reuptake inhibitors. J Am Acad Dermatol 1997;37:281–3.
17 Belch JL. Temperature-associated vascular disorders: Raynaud's phenomenon and erythromelalgia. In: Lowe GD, Tooke JE, eds. A Textbook of Vascu-

lar Medicine. London: Oxford University Press; 1996:339–52.
18 Mork C, Asker CL, Salerud G, Kvernebo K. Microvascular arteriovenous shunting is a probable pathogenetic mechanism in erythromelalgia. J Invest Dermatol 2000;114:643.
19 Stone JD, Rivey MP, Allington DR. Nitroprusside treatment of erythromelalgia in an adolescent female. Ann Pharmacother 1997;31:590–2.
20 Kuhnert SM, Phillips WJ, Davis MD. Lidocaine and mexiltine therapy for erythromelalgia. Arch Dermatol 1999;135:1447–9.
21 Sano S, Itami S, Yoshikawa K. Treatment of erythromelalgia with cyclosporine. N Eng J Med 2003;349:816–7.
22 Rauck RL, Naveira F, Speight KL, Smith BP. Refractory idiopathic erythromelalgia. Anesth Analg 1996;82:1097–101.
23 Davis MP, O'Fallon M, Rogers RS, Rooke TW. Natural history of erythromelalgia Arch Dermatol 2000;136:330–6.