Erythromelalgia: Identification of a corticosteroid-responsive subset

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Background: Corticosteroids (CS) may benefit certain patients with erythromelalgia.

Objectives: Our objective was to determine clinical predictors of corticosteroid-responsive erythromelalgia.

Methods: Patients with erythromelalgia who received CS were identified and stratified into corticosteroid nonresponders (NRs), partial corticosteroid responders (PSRs), complete corticosteroid responders (CSRs), and steroid responders (SRs = PSRs + CSRs). In the study variable analysis, $P < .05$ was considered statistically significant.

Results: The median (interquartile range) age of the 31-patient cohort was 47 years (26-57 years), and 22 (71%) were female. Fourteen (45%) were NRs, 17 (55%) SRs, 8 (26%) PSRs, and 9 (29%) CSRs. A subacute temporal profile to disease zenith (<21 days) was described in 15 (48%) patients, of whom 13 (87%) were SRs ($P = .003$; odds ratio [OR] = 0.069 [95% confidence interval {CI}, 0.011-0.431]). Six (67%) CSRs reported a disease precipitant (eg, surgery, trauma, or infection; $P = .007$; OR = 12.667 [95% CI, 2-80.142]). SR patients received CS sooner than NR at 3 (3-12) versus 24 (17-45) months ($P = .003$). A high-dose CS trial (≥200 mg prednisone cumulatively) was administered to 17 (55%) patients, of whom 13 (76%) were SRs ($P = .012$; OR = 8.125 [95% CI, 1.612-40.752]).

Limitations: This was a retrospective case series.

Conclusion: An infectious, traumatic, or surgical precipitant and subacute presentation may portend CR erythromelalgia. A transient "golden window" where CS intervention is useful may exist before irreversible nociceptive remodeling and central sensitization occurs. (J Am Acad Dermatol 2017;76:506-11.)

Key words: corticosteroids; erythromelalgia; immunotherapy; pain; treatment.

INTRODUCTION

Erythromelalgia is a rare condition that is characterized by the clinical triad of extremity pain, redness, and elevated temperature that occurs at an incidence of 1.3 per million individuals per year.[1] The disorder may be associated with excruciating burning pain in the acral extremities, and typically involves the feet more than the hands symmetrically with paroxysmal symptoms that can more rarely be continuous.[1] Thompson's 5 diagnostic criteria include burning extremity pain, pain aggravated by warming and relieved by cooling, and erythema and increased temperature of affected skin.[2]

Davis et al[3] described the natural history of erythromelalgia in the largest known adult series. During the 8.7-year mean follow-up period, patients improved, worsened, or stayed the same in nearly equal proportions, with only 10.6% of patients experiencing complete symptom abatement. Erythromelalgia was highly disabling and significantly associated with increased mortality and suicide. Medications found to be "very helpful" varied nonpredictably based on

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patient surveys.[3] However, immunosuppressants in the form of either oral corticosteroids (CSs) or plasma exchange had one of the highest rates of a "very helpful" response (33%).[3] Aside from a few case reports describing CS-responsive erythromelalgia among adults, the role of CSs has not been systematically evaluated in a large adult cohort.[4-7]

Oaklander and Klein[8] studied 41 mostly adolescent patients with unexplained, widespread pain syndromes, of whom 9 (23%) had an erythromelalgia phenotype. Among this cohort, 76% had a small-fiber neuropathy and ≤80% of those treated with CSs or intravenous immunoglobulin reported improvement, including some with erythromelalgia. The proportion of patients with erythromelalgia treated and who received CSs versus intravenous immunogloublin were not specifically reported. Dramatic improvement of erythromelalgia after CSs has also been reported in a 12-year-old girl[9] and in 2 patients with acute sensory neuropathy and erythromelalgia.[10]

A potential role for CSs in erythromelalgia has been suggested, and this study was undertaken to define clinical variables predictive of corticosteroid-responsiveness.

CAPSULE SUMMARY

- Erythromelalgia is a highly disabling and often treatment-refractory disease.
- A traumatic, surgical, or infectious erythromelalgia precipitant and subacute temporal profile to disease zenith may predict corticosteroid-responsiveness; corticosteroids may have a transient window of benefit and require higher doses for efficacy.
- Corticosteroids may significantly alter therapeutic decision-making and benefit certain patients with erythromelalgia.

METHODS

After institutional review board approval, the 2000 to 2015 electronic medical record of the Mayo Clinic Rochester was searched to identify patients with erythromelalgia who had received CSs. Patients were only included if the diagnosis of erythromelalgia was confirmed by an expert in this field (ie, JCW, MD, or PS). Patients were excluded if the diagnosis was uncertain or if documentation was inadequate for erythromelalgia symptom response after the CS trial. Within the limitations of a retrospective review, patients were stratified into the following groups based on efficacy: CS nonresponders (NRs), partial CS responders (PSRs), complete CS responders (CSRs), and CS responders (SRs = PSRs + CSRs). PSRs were defined as those with mild to moderate persistence of pain or erythromelalgia symptoms. CSRs were defined as those with absent or minimal pain or erythromelalgia residua after CS administration.

Ancillary diagnostic tests for erythromelalgia included vascular studies, autonomic reflex screening tests (ARSs), thermoregulatory sweat tests (TSTs), electromyography (EMG), and nerve conduction studies (NCSs). Vascular studies measured skin temperature, blood flow, and transcutaneous oximetry. ARSs and TSTs test for small-fiber neuropathy. The ARS included a 4-point sweat test, heart rate variability analysis to Valsalva and deep breathing, Valsalva-mediated blood pressure changes, and tilt-table testing.[11,12] The TST was performed by giving a controlled heat stimulus to the whole body using powder that turns dark purple on perspiring skin.[13] EMG and NCSs were performed to assess large-fiber nerves.[14]

Clinical and diagnostic variables were collected, including demographics, comorbidities, medications, erythromelalgia rate of onset, duration, body location and precipitants, CS type, dose and duration, and electrophysiologic studies. Variables were analyzed for statistical significance using JMP statistical software (version 11; SAS Institute, Cary, NC). The NR group was directly compared with the SR, PSR, and CSR subgroups for statistical association. For continuous variables, t and Wilcoxon rank sum nonparametric tests were used for Gaussian and non-Gaussian variables, respectively. The Fisher's exact test was used to analyze dichotomized variables. $P < .05$ was considered statistically significant.

RESULTS

Epidemiology and disease characteristics

Table I provides a detailed summary of epidemiologic and clinical variables. Thirty-one patients with a diagnosis of erythromelalgia were enrolled in a CS immunotherapy trial. The median (interquartile range) age of the entire cohort was 47 years (26-57 years), of whom 22 (71%) were female. Fourteen (45%) patients had no response to CSs and were identified as NRs. The remaining 17 (55%) patients were SRs and were subdivided into 8 (26%) PSRs and 9 (29%) CSRs. The NRs and SRs did not differ in age. SRs were diagnosed with erythromelalgia after symptom onset earlier than

Abbreviations used:

ARS:	autonomic reflex screening test
CS:	corticosteroid
CSR:	complete corticosteroid responder
EMG:	electromyography
HDIT:	high-dose immunotherapy trial
NCS:	nerve conduction study
NR:	corticosteroid nonresponder
PSR:	partial corticosteroid responder
SR:	corticosteroid responder
TST:	thermoregulatory sweat test
VHDIT:	very-high dose immunotherapy trial

NRs at 6 months (3-32 months) versus 24 months (24-36 months; $P = .009$).

Erythromelalgia presented most commonly as a lower extremity, distal predominant phenotype in 15 (48%) patients, although varying, stereotyped presentations involving the hands and face also occurred (Table I).

The temporal profile of erythromelalgia onset was strikingly different between the patients who did and did not respond to CS. A subacute temporal profile, defined as disease crescendo to peak intensity in <21 days, was described in 15 (48%) patients overall, of whom 2 (13%) were NRs compared to 13 (87%) SRs ($P = .003$; odds ratio [OR] = 0.069 [95% confidence interval {CI}, 0.011-0.431]). Eight (89%) of 9 CSRs presented in a subacute fashion.

An inciting clinical event, such as an antecedent surgery, infection, or localized body trauma, was felt to have precipitated erythromelalgia in 9 (29%) patients overall, of whom 7 (78%) were SRs. Six (67%) of 9 CSRs reported such a precipitant ($P = .007$; OR = 12.667 [95% CI, 2-80.142]; Table II).

An autoimmune diathesis was common in our cohort, but was not significantly different between NR and SR groups (Supplemental Table I; available online at http://www.jaad.org). Polycythemia vera was found in 2 (6%) patients and both were NRs. Interestingly, 2 patients who presented subacutely were diagnosed with malignancy shortly after the diagnosis of erythromelalgia, raising the specter of a paraneoplastic association. After erythromelalgia onset, 1 patient had multiple myeloma diagnosed at 3 months and 1 patient had chronic myelogenous leukemia diagnosed at 18 months.

Diagnostic data

Neurologic examination suggested a large- or small-fiber neuropathy, in 9 (35%) of 26 patients overall. EMG confirmed a large-fiber neuropathy in 6 (27%) of 22 patients. ARS was abnormal in 15 (68%) of 22 patients and TST abnormal in 18 (75%) of 24 patients, confirming a common small-fiber neuropathy association. Vascular studies were abnormal in 13 (59%) of 22 patients.

Corticosteroid treatment data

Patients had attempted a mean of 5.7 ± 3.5 adjuvant medications for their pain with inadequate pain control before a CS trial. The duration of time from erythromelalgia symptom onset to CS trial was 12 months (range, 3-28 months) overall and significantly shorter in SR compared to NR groups, with 3 months (range, 3-12 months) versus 24 months (range, 17-45 months), respectively ($P = .003$; Table III). The CSR group had a shorter mean time to CS trial compared to PSRs, with 3 months (range, 3-4 months) compared to 8 months (range, 3-17 months), respectively.

Doses and durations of the oral CS regimen varied significantly between patients. A high-dose immunotherapy trial (HDIT) was defined as prednisone 40 mg or greater CS equivalent administered daily over ≥5 days (ie, ≥200 mg prednisone). A very HDIT (VHDIT) was defined as the subset of HDIT receiving methylprednisolone 1000 mg administered for ≥5 doses (ie, ≥5000 mg methylprednisolone). HDIT was administered to 17 (55%) patients, of whom 13 (76%) were SRs and 4 (29%) NRs ($P = .012$; OR = 8.125 [95% CI, 1.612-40.752]). VHDIT was administered to 10 (32%) patients, of whom 8 (80%) were SRs. VHDIT was administered to 6 (67%) of 9 CSRs ($P = .015$; OR = 9 [95% CI, 1.550-52.266]).

DISCUSSION

We report and characterize a CS responsive subgroup of patients with erythromelalgia. Our findings are concordant with a pediatric pain population that included a subset of CS responsive patients with erythromelalgia where 61% of families reported an antecedent systemic illness or precipitating trauma.[8] In our cohort, 94% of patients were adults. Inflammatory neuropathy, such as Guillain–Barré syndrome, can be precipitated by infection (eg, *Campylobacter jejuni*), and acute small-fiber sensory neuropathy with erythromelalgia may be a variant.[15] In another report, a 20-year-old man developed a severe, fulminant erythromelalgia 5 hours after spraining his ankle and responded to methylprednisolone.[16] Although surgery has not been previously reported as an erythromelalgia precipitant, 4 of our patients had a temporally associated surgical trigger. Other forms of post-surgical inflammatory neuropathy have been well characterized in the literature, with evidence of microvasculitis on after obtaining a nerve biopsy specimen and probable CS responsiveness.[17,18]

Table I. Epidemiology and disease characteristics

Clinical variables	Total (n = 31)	NRs (n = 14)	SRs (n = 17)	PSRs (n = 8)	CSRs (n = 9)	*P* value
Median age, y (IQR)	47 (26-57)	49 (41-65)	38 (25-51)	41 (24-50)	38 (25-55)	NS
Female sex, n (%)	22 (71)	10 (71)	12 (70)	7 (88)	5 (56)	NS
Precipitant identified,* n (%)	9 (29)	2 (14)	7 (41)	1 (13)	6 (67)	.132†
Subacute onset,‡ n (%)	15 (48)	2 (13)	13 (87)	5 (62.5)	8 (89)	.003
Median months to diagnosis (IQR)	24 (5-36)	24 (24-36)	6 (3-32)	11 (4-21)	4 (2-60)	.009
No. of pain medications, mean ± SD	5.7 ± 3.5	6.2 ± 4.1	5.2 ± 2.9	4.8 ± 1.4	5.75 ± 3.7	NS
Severe life impact, n (%)	17 (55)	6 (43)	10 (59)	7 (88)	3 (33)	NS
Median months since follow-up§ (IQR)	14 (5-27)	11 (4-22)	18 (7-47)	15 (2-26)	18 (8-47)	NS
Comorbidities, n (%)						
Autoimmune history‖	15 (48)	7 (50)	8 (47)	4 (50)	4 (44)	NS
Autoimmune laboratory values	12 (39)	5 (36)	7 (41)	3 (38)	4 (44)	NS
Autoimmune diathesis¶	17 (55)	7 (50)	10 (59)	5 (63)	5 (56)	NS
Polycythemia vera	2 (6)	2 (14)				NS
Paraneoplastic erythromelalgia#	2 (6)	0	2 (12)	1 (13)	1 (11)	NS
Tobacco use	8 (26)	3 (21)	5 (29)	4 (50)	1 (11)	NS
Involvement by body region, n (%)						
Feet	30 (97)	14 (100)	16 (94)	7 (88)	9 (100)	NS
Hands	15 (48)	5 (36)	10 (59)	5 (63)	5 (56)	NS
Face	8 (26)	5 (36)	3 (18)	3 (38)	0	NS
Clinical presentation(s), n (%)						
Lower extremity, distal predominant	15 (48)	9 (64)	6 (35)	2 (25)	4 (44)	NS
Upper extremity, distal predominant	1 (3)	—	1 (6)	1 (13)	—	NS
Distal appendicular, mainly hands and feet	6 (19)	—	6 (35)	1 (13)	5 (56)	.021
Diffuse, mainly hands, feet, and face	8 (26)	5 (36)	3 (18)	3 (38)	—	NS
Legs and torso	1 (3)	—	1 (6)	1 (13)	—	NS

CSR, Complete corticosteroid responder; *IQR*, interquartile range; *NR*, corticosteroid nonresponder; *NS*, not significant; *PSR*, partial corticosteroid responder; *SD*, standard deviation; *SR*, steroid responder.

*Defined as an antecedent surgery, infection, or localized body trauma felt to have precipitated erythromelalgia.

†When analyzing the CSR group alone compared to NRs, statistical significance is achieved ($P = .007$).

‡Defined as disease crescendo to peak intensity in <21 days.

§Defined as last visit in months after first clinical encounter.

‖Autoimmune is used as an umbrella term to encompass both autoimmune and also inflammatory, but perhaps not strictly autoimmune, states.

¶Defined as a patient having a medical history, significant family history, or serologic evidence of an autoimmune or inflammatory condition.

#One patient had chronic myelogenous leukemia and 1 had multiple myeloma diagnosed shortly after the diagnosis of erythromelalgia.

SR patients could have presented sooner than NR patients because of more fulminant disease. Alternatively, NR may have been more difficult to diagnose because of a different disease presentation. However, a "golden window" may exist in some patients; if not treated promptly enough, irreversible damage to peripheral nociceptors with neuropathic sensitization may occur. Chronic neuropathic pain has been shown to involve morphologic changes at the cutaneous nociceptor level histologically, thereby perpetuating the chronic pain process.[19] There could exist a time-dependency between the 2 ends of this spectrum, with an initially reversible process becoming irreversible in the presence of untreated disease.

HDIT was significantly associated with CS responsiveness. Nearly all CSR patients received HDIT; most of those received VHDIT. It is possible that more patients could have responded to CS if a higher dose had been administered. Importantly, while a CS responsive cohort of erythromelalgia has been reported amongst a larger group of pediatric pain patients with a small-fiber neuropathy,[8] in our cohort age did not influence treatment responsiveness. A CS trial might be justifiable in many patients with erythromelalgia regardless of age, particularly early in the disease course, in the event that an ephemeral "golden window" exists where CS intervention is effective. However, not all patients respond to CS, and these patients may benefit from other topical and oral symptomatic treatments as previously described.[3]

Paraneoplastic erythromelalgia has been reported in association with solid tumors and patients with chronic myelogenous leukemia.[20] To our knowledge, paraneoplastic erythromelalgia has not previously been reported in association with multiple myeloma. Given the treatment ramifications,

Table II. Disease precipitants

Patient no.	Age, y	Sex	Corticosteroid response	Precipitant	Description
1	18	M	CSR	Surgery	Bilateral hip labral repair and femoral head and neck junction osteoplasty, followed by an immediate, transient, bilateral postoperative sciatic distribution sensorimotor dysfunction that was followed 4 weeks later by an acute, severe erythromelalgia
2	18	F	CSR	Surgery	Arthroscopic knee surgery, developed erythromelalgia while convalescing in the hospital
3	35	F	CSR	Infection	Fever, myalgia, arthralgia, edema, and a biopsy-confirmed cutaneous vasculitis with a subacute onset, self-limiting erythromelalgia that recurred severely 1 year later during the second trimester of pregnancy
4	38	F	CSR	Trauma	Localized toe trauma while cleaning an attic and developed erythromelalgia in the injured toes days later
5	63	M	CSR	Surgery	Surgery not described, developed erythromelalgia in the postoperative setting
6	69	M	CSR	Trauma	Traumatic left Achilles tendon rupture with surgical repair followed by initially left-foot predominant erythromelalgia 3 months later
7	27	F	PSR	Trauma	Injured left toe in the bathtub, followed by a severe, localized erythromelalgia that spontaneously subsided and then recurred 1 year later in all of her left toes
8	42	M	NR	Surgery	Vein stripping 2 weeks previously, followed by gradual, slow onset, foot-predominant erythromelalgia
9	44	F	NR	Infection	"Stomach flu" a few weeks beforehand, no other documentation

CSR, Complete corticosteroid responder; *F*, female; *M*, male; *NR*, corticosteroid nonresponder; *PSR*, partial corticosteroid responder.

Table III. Immunotherapy treatment data

Clinical variables	Total (n = 31)	NRs (n = 14)	SRs (n = 17)	PSRs (n = 8)	CSRs (n = 9)	*P* value
Median no. of months to CS trial (IQR)	12 (3-28)	24 (17-45)	3 (3-12)	8 (3-17)	3 (3-4)	.003
HDIT, n (%)	17 (55)	4 (29)	13 (76)	6 (75)	7 (78)	.012
VHDIT, n (%)	10 (32)	2 (14)	8 (47)	2 (25)	6 (67)	.015*
Maintenance immunotherapy, n (%)	12 (39)	2 (14)†	10 (59)	5 (63)‡	5 (56)§	.011

CS, Corticosteroid; *CSR*, complete corticosteroid responder; *HDIT*, high-dose immunotherapy trial; *IQR*, interquartile range; *MCTD*, mixed connective tissue disease; *NR*, corticosteroid nonresponder; *NS*, not significant; *PSR*, partial corticosteroid responder; *SR*, corticosteroid responder; *VHDIT*, very high-dose immunotherapy trial.

*When analyzing the CSR group alone compared to NRs, statistical significance is achieved ($P = .015$).

†One patient was treated for lupus and 1 for MCTD.

‡Two patients received HDIT for erythromelalgia flares, and each had a partial response. Three patients received hydroxychloroquine or methotrexate for lupus and MCTD.

§One patient required monthly VHDIT indefinitely, and 1 patient required a second HDIT for erythromelalgia recrudescence. One patient received chemotherapy for multiple myeloma and 2 patients received HDIT for Blau syndrome and MCTD.

paraneoplastic erythromelalgia should be considered in patients with erythromelalgia cases who present subacutely.

Study strengths include patient evaluation by experts in erythromelalgia and painful neuropathies and the use of advanced adjuvant diagnostic testing. Erythromelalgia diagnosis was made with a high degree of confidence and uncertain cases were excluded, limiting false-positive errors. Our study population is sizeable given the rare nature of erythromelalgia. Given our status as a tertiary care referral center, our patient population could have been skewed toward a more refractory, severe, and prolonged erythromelalgia. As a result, our data could have possibly understated the potential value of CS in patients with erythromelalgia.

Study limitations include the retrospective design and investigator bias inherent to any single-center study. While HDIT was associated with CS responsiveness in our series, the relationship between cumulative CS dose and treatment effect cannot be proven with a retrospective study design. Insufficient documentation prevented a study of the effect of short versus extended duration treatment

protocols, and systematic, objective measures of erythromelalgia symptom burden after CS administration were not available retrospectively. The smaller sample size could have led to false-negative errors because of insufficient power. A monophasic disease course as a confounder cannot be excluded, meaning that the CS effect could be coincidental; however, the immunotherapy dependency in nearly half of the SR cohort and the clear temporal relationship of improvement with CS intervention militates against a confounder effect.

In conclusion, erythromelalgia is a severely disabling syndrome with significant morbidity and increased mortality and suicide rates. We report a clinically important subset of erythromelalgia that is CS responsive and have potentially defined patients who are most likely to respond to a CS trial. A clear infectious, traumatic, or surgical precipitant and a subacute disease presentation may portend CS responsive erythromelalgia. CS responsiveness is not influenced by age, examination findings, or the results of ancillary testing, although these are useful for establishing a diagnosis. There may be a transient, time-dependent, "golden window" where CS intervention is useful before irreversible nociceptive remodeling and central sensitization occurs. If considered, therefore, a CS trial should be performed early in the course of erythromelalgia. A HDIT or VHDIT CS regimen should be used for the initial CS trial, with duration to be guided by symptom responsiveness. A subacute erythromelalgia can be paraneoplastic in origin, and such etiologies bear diagnostic consideration before initiating an immunosuppressive trial.

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Supplemental Table I. Autoimmune findings

	Total (n = 31)	NRs (n = 14)	SRs (n = 17)	PSRs (n = 8)	CSRs (n = 9)	*P* value
Autoimmune diagnoses, n (%)						NS
Hypothyroidism	3 (10)	2 (14)	1 (6)	1 (12)		
Connective tissue disease, NOS	2 (6)	1 (7)	1 (6)	1 (12)		
Raynaud syndrome	2 (6)	1 (7)	1 (6)		1 (11)	
Systemic lupus erythematosus	2 (6)	1 (7)	1 (6)		1 (11)	
Myasthenia gravis	1 (3)	1 (7)				
Pernicious anemia	1 (3)	1 (7)				
Gastroparesis, idiopathic	1 (3)	1 (7)				
Diabetes mellitus, type I	2 (6)		2 (12)	1 (12)	1 (11)	
Rheumatoid arthritis	1 (3)		1 (6)	1 (12)		
Livedoid vasculopathy	1 (3)		1 (6)	1 (12)		
Blau syndrome with Crohn's disease	1 (3)		1 (6)		1 (11)	
Spondyloarthropathy	1 (3)		1 (6)		1 (11)	
Autoimmune serologies, n (%)						NS
Antinuclear antibody	9 (29)	3 (21)	6 (35)	3 (37)	3 (33)	
dsDNA	2 (6)	1 (7)	1 (6)	1 (12)		
TPO	2 (6)	1 (7)	1 (6)		1 (11)	
SS-A (Ro)	1 (3)	1 (7)				
AChRAb	1 (3)	1 (7)				
C-reactive protein	2 (6)		2 (12)	1 (12)	1 (11)	
Rheumatoid factor	1 (3)		1 (6)	1 (12)		
HLAB27	1 (3)		1 (6)		1 (11)	
Hematologic, n (%)						NS
SPEP/SPIF	3 (10)	1 (7)	2 (12)	1 (12.5)	1 (11)	
Polycythemia vera	2 (6)	2 (14)				
CML	1 (3)		1 (6)		1 (11)	
Multiple myeloma	1 (3)		1 (6)		1 (11)	

AChRAb, Nicotinic acetylcholine receptor antibody; *ANA*, antinuclear antibody; *CML*, chronic myelogenous leukemia; *CSR*, complete steroid responder; *dsDNA*, double-stranded DNA antibody; *HLAB27*, human leukocyte antigen B27; *NOS*, not otherwise specified; *NS*, not significant; *PSR*, partial steroid responder; *SNR*, steroid nonresponder; *SPEP/SPIF*, serum protein electrophoresis and immunofixation (monoclonal protein study); *SR*, steroid responder; *SS*-A, Sjögren antibody; *TPO*, thyroid peroxidase antibody.