Natural history of Erythromelalgia: presentation and outcome in 168 patients.

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Objective: To describe the demographics, presentation, and outcome in patients with erythromelalgia-a rare and poorly understood clinical syndrome defined by the triad of red, hot, painful extremities.

Design: Retrospective medical record review with follow-up by survey questionnaire. Setting: Large tertiary care medical center.

Subjects: Patients with erythromelalgia examined at the Mayo Clinic, Rochester, Minn, between 1970 and 1994.

Intervention: The medical records of 168 patients were analyzed. Follow-up data, which consisted of answers to 2 survey questionnaires or the most recent information in the medical record from patients still alive and death certificates or reports of death for those deceased patients, were obtained for all but 13 patients.

Main Outcome Measures: Survival, morbidity, and quality of life.

Results: All patients were white; 122 (72.6%) were female, and 46 (27.4%) were male. At presentation, the patients' mean age was 55.8 years (age range, 5-91 years). Symptoms had been present since childhood in 7 patients (4.2%). Six patients (3.6%) had a first-degree relative with erythromelalgia. Symptoms were intermittent in 163 patients (97.0%) and constant in 5 (3.0%). Symptoms predominantly involved feet (148 patients [88.1%]) and hands (43 patients [25.6%]). Kaplan-Meier survival curves revealed a significant decrease in survival compared with that expected in persons of similar age and of the same sex (P<.001). After a mean follow-up of 8.7 years (range, 1.3-20 years), 30 patients (31.9%) reported worsening of, 25 (26.6%) no change in, 29 (30.9%) improvement in, and 10 (10.6%) complete resolution of the symptoms. On a standard health status questionnaire, scores for all but one of the health domains were significantly

diminished in comparison with those in the US general population.

Conclusion: Erythromelalgia is a syndrome with significantly increased mortality and morbidity compared with the US general population.

ERYTHROMELALGIA is a rare clinical syndrome characterized by the triad of redness, increased temperature, and pain usually of the extremities. The term erythromelalgia was coined in 1878 by Mitchell.[1] erythros (red), melos (extremity), and algos (pain). Other terms have been used, [2,3] such as "erythermalgia"' and "erythralgia." Babb et al ,[5] in an article describing 51 patients from our institution in 1964, suggested that an increased incidence of myeloproliferative disease was associated with the disorder.

To better define the demographics, presentation, role of therapy, and outcome of erythromelalgia, we studied patients with erythromelalgia examined at the Mayo Clinic, Rochester, Minn, between 1970 and 1994. This is the largest retrospective study of the syndrome of erythromelalgia thus far reported describing patients with the diagnosis of erythromelalgia.
We provide the first available data on the natural history of disease and quality-of-life measures in these patients and demonstrate that erythromelalgia is a clinical syndrome associated with significant mortality and morbidity.

RESULTS

PATIENT DEMOGRAPHICS

One hundred sixty-eight patients with disease fulfilling the diagnosis of erythromelalgia were seen at the Mayo Clinic between 1970 and 1994; 122 (72.6%) were female, and 46 (27.4%) were male. All were white. Average age of these patients was 55.8 ± 18.9 years; median age, 60 years; and age range, 5 to 91 years. Three patients were 11 years old or younger.

Fifteen patients were from Olmsted County, Minnesota, and 32 from elsewhere in the State of Minnesota. Incidence could not be calculated, because we did not screen other possible codings of the disorder and thus could not be sure of complete population-based case assessment.

Six patients (including 3 from 1 family) had a first degree relative with erythromelalgia. Two more patients have since reported a first-degree relative with the disorder.

PATIENTS, MATERIALS, AND METHODS

Patients With Erythromelalgia The medical records of 271 Mayo Clinic patients with a master index diagnosis of erythromelalgia between 1970 and 1994 were reviewed. Erythromelalgia was defined as a convincing history of unexplained red, hot, and painful extremities. The subjective elements of redness, heat, and pain were required to fulfill the diagnosis. Because of the intermittent nature of this disorder, it was impossible to demonstrate objective signs in some patients. One hundred sixty eight cases fulfilled these criteria for inclusion in the study.

Data Abstracted The history of erythromelalgia at presentation, duration of disease at presentation, associated illnesses at presentation, characteristics of the presentation, distribution of the disease, laboratory results, and findings on clinical examination were recorded and compared.

Follow-Up Follow-up of all patients was attempted. When necessary, death certificates were obtained, or the cause of death was established by contacting the deceased's family by telephone or mail.
All living patients were sent 2 survey questionnaires (an erythromelalgia survey questionnaire and a health survey questionnaire) by the Mayo Survey Research Center. If there was no reply to a first or second mailing, contact was made by telephone. If a patient signed a letter refusing to fill out the surveys (10 patients did so), the patient was documented as being alive on that date for the Kaplan-Meier survival curves. If the patient could not be traced, the latest follow-up in the clinic medical record within the past 2 years was reviewed. If there was no follow-up within that time, the patient was deemed to have been lost to follow-up and was excluded from compilation of the Kaplan-Meier survival curve.

Erythromelalgia Survey Questionnaire The questions covered symptoms, coincident diseases, quality of life., and the effectiveness of various treatments tried.

Health Survey Questionnaire Along with the erythromelalgia survey questionnaire, a general health questionnaire (Medical Outcome Survey Short Form 36-Items [SF-36])[6] was sent to the patients. The SF-36 is a self'-administered standard survey that measures health related quality-of-life outcomes that are not specific to age, disease, or treatment and that are known to be most directly affected by disease and treatment. It provides a common yardstick to compare patients who have chronic health problems with those

sampled from the US general population. United States general population norms were estimated from responses to the National Survey of Functional Health Status, a 1990 cross-sectional survey that included the SF-36. Respondents were drawn from the sample frames of the 1989 and 1990 reports of the General Social Survey, conducted by the National Opinion Research Center. The General Social Survey has surveyed the non-institutionalized, adult US population annually over the past 20 years.[6] Physical and mental health concepts are measured. The SF-36 includes 1 multi-item scale measuring each of 8 health concepts (or domains): (l.) physical functioning, (2) role limitations due to physical health problems, (3) bodily pain, (4) general health, (5) vitality (energy and fatigue), (6) social functioning, (7) role limitations due to emotional problems, and (8) mental health (psychological stress and psychological well-being). These scales were scored by the 5-point Likert scale.

The SF-36 was scored so that a higher score indicated a better state of health. The scores were compared with scores from persons from the US general population. The SF-36 has been validated, and there are at least 260 clinical trials using the. SF-36 to assess general health outcomes from the patient's viewpoint.[7]

Statistical Analyses

Appropriate summary statistics (eg, means, medians, SEs, and SDs) were used to describe these data. Kaplan-Meier survival curves were obtained to estimate survival from diagnosis. A 1-sample log rank test was performed to test survival compared with that expected for persons of similar age and same sex with use of 1980 Minnesota white reference rates. The Cox proportional hazards model was used to assess the influence that certain characteristics at diagnosis had on survival. Statistical significance was set at $P<.05$. All values are reported as mean ± SD.

Neurophysiological And Vascular Studies

We assessed the frequency and types of abnormalities observed during tests of vascular, peripheral neurophysiological, and autonomic function in patients with erythromelalgia. These will be reported in detail in a separate article.[8] Briefly, 5 patients had detailed vascular studies performed in 10 affected lower extremities before and during symptoms. Fifty-four patients underwent neurophysiological testing, 27 had autonomic reflex screening, and 2 had recordings of peripheral autonomic surface potentials.

CLINICAL PRESENTATION

At the time of presentation, the average duration of symptoms varied from less than I month to 26 years (mean, 47.6 t 59 months; median, 24 months). Symptoms had been present since childhood in 7 patients (4.2%). Symptoms were intermittent in 163 patients (97.0%) and constant in 5 (3.0%). Feet were involved in 148 (88.1%), hands in 43 (25.6%), and legs in 23 (13.7%). Other sites involved were ears (1 patient), neck (1 patient), and face (4 patients).

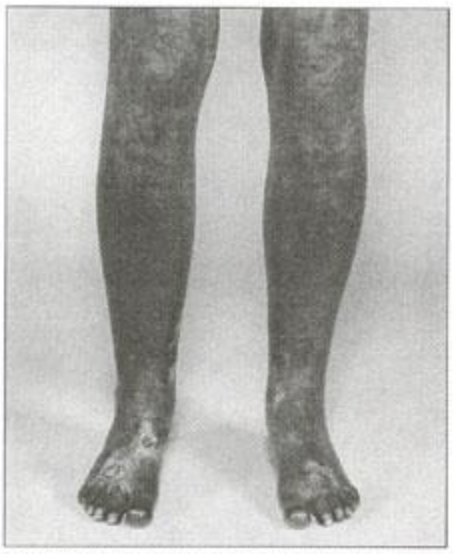

Figure 1. *Patient with red, hot, and painful extremities of erythromelalgia.*

During symptoms, the painful affected extremity was described as "hot" by 81 patients (48.2%), "burning" by 110 (65.5%), and "numb" by 5 (3.0%).
Symptoms were exacerbated by heat in 86 patients (51.2%) and exercise in 48 (28.6%), and they were worse at night in 42 (25.0%). Cooling the extremity with cold water or ice relieved the symptoms in 113 (67.3%).

On physical examination, the affected limb was abnormal in 111 patients (66.1%) and normal in 57 (33.9%). The affected limb was red in 83 (49.4%) (Figure 1) and manifested acrocyanosis in 16 (9.5%), ulcers in 10 (6.0%), and a reticular cutaneous pattern in 8 (4.8%). Gangrene was not seen.

COMORBIDITIES

A history of smoking was present in 84 patients (50%), of hypertension in 23 (1.3.7%), of hyperlipidemia in 19 (11.3%), and of diabetes mellitus in 4 (2.4%). A history of myeloproliferative disease was present in 15 patients (8.9%): polycythemia rubra vera in 9, essential thrombocythemia in 4, and chronic granulocytic leukemia in 2.

INVESTIGATIONS

Erythrocyte sedimentation rate, determined in 136 patients, was increased (defined as >29 mm/h) in 11 patients (8.1%). Serum protein electrophoresis was performed in 111 patients, and findings were abnormal in 4 (3.6%). A skin biopsy specimen was obtained in l.2 patients (7.1%); all specimens were reviewed, and the findings were confirmed as variable and nonspecific.

Table 1. Cause of Death in 45 Patients With Erythromelalgia

Cause	No. of Patients
Unknown	12
Cardiovascular	11
Myeloproliferative disease	6
Solid cancers (all)	5
Lung	2
Breast	1
Prostate	1
Ovarian	1
Suicide	3
Accidents	2
Connective tissue disease	2
Pulmonary	2
Cerebrovascular	1
Gastrointestinal hemorrhage	1

Results of vascular and neurophysiological studies will be reported in a separate article.'8] Briefly, measurements in the toes during symptoms revealed a mean temperature increase of 11.6°C (P<001) along with a laser flow increase from a mean of 6.8 mL/min per 100 g of tissue to 76.5 mL/min per 100 g of tissue (P<.001). Baseline transcutaneous oximetry measurements (TcP0z) in the feet decreased by 6.7 mm Hg (P = .03) during symptoms. Twenty-one of 54 electromyographic recordings showed abnormalities: all fulfilled the criteria for axonal neuropathy. Seventeen of 27 autonomic reflex screening tests and 1 test of peripheral autonomic surface potentials showed severe postganglionic sudomotor impairment; 5 of 17 patients additionally had peripheral adrenergic dysfunction.

FOLLOW-UP

Demographics

Ninety-nine patients (58.9%) completed the erythromelalgia survey questionnaire; 98 patients completed the SF-36 health survey questionnaire. The questionnaires were completed a mean of 8.7 years after the diagnosis (range, 1.3-20 years). Forty-five patients (26.8%) were ascertained to be dead in 1996. Eleven patients (6.5%) who did not complete the questionnaire had adequate recent follow-up data available in their clinical records. No follow-up data were available for 13 patients (7.7%). These patients were seen only once and could not be reached for final follow-up.

Death

The causes of death are listed in Table 1. Death occurred a mean of 6.3 ± 4.8 years (range, 0.44-18.84 years) after the diagnosis. Copies of death certificates were obtained for 27 patients. Three of the patients in our study committed suicide because of their disease. Additionally, an affected relative of 1 patient committed suicide.

Kaplan-Meier Survival Curve

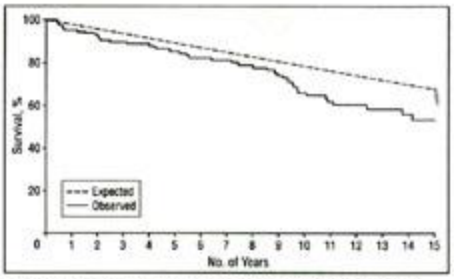

Figure 2. *Expected vs observed survival (Kaplan-Meier) in patients with erythromelalgia. At 15 years, 95% confidence interval equals 42.8, 65.9.*

The Kaplan-Meier survival estimates are shown in Figure S. A 1-sample log rank test showed a significant decrease in survival from that expected in persons of similar age and of the salve sex on the basis of 1980 Minnesota white reference rates (P<.001). We studied 4 factors recorded at the time of diagnosis: sex, age, duration of symptoms, and smoking. There was no statistically significant difference in survival rates between males and females (P = .12). Older patients had a significantly higher risk of death (P<.001), with the risk increasing 4% (95% confidence interval, 1%-6%) per year of age. When age at diagnosis was adjusted for, sex, duration of symptoms, and smoking were not statistically significant.

Erythromelalgia Survey Questionnaire

Symptom Progression. Patients were asked whether their symptoms had progressed since their initial Mayo Clinic visit. Thirty (31.9%) of 94 reported that in general their symptoms were worse; 25 (26.6%), that they were about the same; 29 (30.9%), that they had decreased; and 10 (10.6%), that they had disappeared completely.

When asked specifically about how their symptoms had changed, 25 (26.6%) reported that the episodes of erythromelalgia were "a lot more frequent;" 8 (8.5%), that they were "somewhat more frequent;" 23 (24.5%), that they were "about the same;" 10 (10.6%), that they were "somewhat less frequent;" 18 (19.1%), that they were "a lot less frequent," and 10 (10.6%), that their symptoms had "completely stopped."

Eighty-two (85.4%) of 96 patients reported episodes of erythromelalgia within the previous 12 months. Only 43 (43.4%) of 99 patients reported average annual frequencies of symptoms. The average rate was 72 episodes per person-year, or 1.38 episodes per week.

Distribution of Symptoms. Of 63 patients (63.6%) with symptoms involving only the lower extremities at presentation, 9 (14.3%) reported progression to involvement of upper and lower extremities. No such progression was reported by patients with upper extremity symptoms alone at presentation. Of the 5 patients with unilateral symptoms at presentation, only 1 reported progression to bilateral symptoms.

Local Complications. Eighty-seven patients answered the question on local complications. Unspecified skin damage due to ice or cold water (19 patients [21.8%]), infections (14 [16.1%]), ulcers (11 [12.6%]), and development of gangrene (1 [1.1% >]) were reported. No patients reported amputation or loss of a limb.

Functional Impairment. Reported disabilities attributed to erythromelalgia included

inability to walk long distances (48 patients t50.0%1), inability to stand for long periods (47 [49.0%]), having to give up a job (12 [12.5%]), inability to drive (12 [12.5%]), use of a wheelchair (3
[3.1%]),and being bed bound (2 [2.1%]).

Associated Myeloproliferative Disease. Myeloproliferative disease was reported to have developed later in 2 (1.3%) of the 153 patients who did not have it at presentation (chronic myeloid leukemia in one patient and polycythemia rubra vera in the other).

Efficacy of Treatment. The patients responding to the survey questionnaire tried 84 different drugs or methods of treatment to relieve their symptoms. The effectiveness of the most commonly tried treatment categories (any tried by at least 2 patients) is summarized in Table 2.

Table 2. Reported Response to the Most Commonly Used Medications and Treatments in 99 Patients With Erythromelalgia*

Drug or Treatment Class	No. of Patients	Response, % of Patients: Very Helpful	Somewhat Helpful	Not Helpful
Aspirin	57	17.5	29.8	52.6
Nonsteroidal anti-inflammatory drugs (ibuprofen, indomethacin, nabumetone, naproxen, or sulindac)	49	18.4	30.6	51.0
β-Blockers (atenolol, nadolol, propranolol hydrochloride, or timolol)	40	22.5	20.0	57.5
Antihistamines (cyproheptadine hydrochloride, or diphenhydramine, phenylpropanolamine, trimeprazine, or cimetidine)	28	10.7	14.3	75.0
Physical methods (biofeedback, epidural blocks, hypnosis, or TENS† unit)	23	17.4	26.1	56.5
Vasodilators (nitroglycerin, nitroprusside, nicotinic acid, nifedipine, diltiazem)	20	10.0	5.0	85.0
Capsaicin	16	12.5	6.3	81.2
Anticonvulsants (carbamazepine or phenytoin)	13	15.4	23.1	61.5
Antidepressants (chlorpromazine, amitriptyline, thioridazine, nortriptyline, fluphenazine, doxepin)	12	16.7	25.0	58.3
Immunosuppressants (oral corticosteroids or plasma exchange)	12	33.3	8.3	58.4
Antimigraine (ergotamine or methysergide)	10	10.0	10.0	80.0
Pentoxifylline	9	22.2	11.1	66.7
Dipyridamole	7	14.3	14.3	71.4
Sympathetic nerve interruption (surgical sympathectomy, chemical sympathectomy, or phenoxybenzamine)	6	0	50.0	50.0
Mexiletine hydrochloride	5	0	40.0	60.0
Antimitotics (busulfan, hydroxyurea, or radioactive phosphorus)	4	75.0	25.0	0
Clonidine	4	0	25.0	75.0
α-Blockers (prazosin)	3	33.3	33.3	33.3
Quinine sulfate	3	0	33.3	66.6
Muscle relaxants (carisoprodol)	2	0	50.0	50.0

*Data derived from erythromelalgia survey questionnaire.
†TENS indicates transcutaneous electrical nerve stimulation.

Table 3. Summary of Results From 98 Patients With Erythromelalgia Who Responded to the Health Status Questionnaire (HSQ)

HSQ Scale	Standardized Scores*: Mean ± SD	Median (Range)	P†	Patients With Abnormal Scores, %‡
Mental health	-0.2 ± 1.0	0.1 (-3.6 to 1.5)	.13	6
Energy/fatigue	-0.4 ± 0.9	-0.3 (-2.8 to 2.0)	<.001	6
Role limitations: emotional problems	-0.2 ± 1.2	0.6 (-3.2 to 0.7)	.04	14
Health perception	-0.5 ± 1.3	-0.5 (-4.1 to 1.7)	<.001	14
Role limitations: physical health	-0.9 ± 1.4	-1.2 (-4.4 to 1.0)	<.001	19
Physical functioning	-0.9 ± 1.7	-0.6 (-6.2 to 1.3)	<.001	22
Social functioning	-0.7 ± 1.4	-0.5 (-4.0 to 0.9)	<.001	18
Bodily pain	-0.7 ± 1.3	-0.7 (-3.8 to 1.3)	<.001	15

*Standardized scores = $(x_i - k)/SD_r$. In this equation, x_i is the patient's score, k_i is the mean of the reference sample for persons of similar age (5-year age group) and sex, and SD_r is the SD for the reference sample for persons of similar age and sex. A standardized score of −2.00 means that this patient is 2 SDs below the age- and sex-comparable reference sample peers.
†One-sample, 2-tailed t test P value comparing the mean standardized score to the normative reference mean of zero.
‡Percentage of patients who obtained a standardized score of −2.00 or less.

SF-36 HEALTH SURVEY QUESTIONNAIRE

Ninety-eight health survey questionnaires were received from the patients contacted, and the results of this questionnaire were compared with the scores obtained from a cohort from the US general population (Table 3). Respondents obtained mean standardized scores significantly lower (poorer) than the reference mean of 0 in all 8 SF-36 domains. The physical functioning domain had the greatest percentage of patients (22%) scoring in the abnormal range; the mental health and vitality domains had the

fewest patients scoring in the abnormal range (6%).

COMMENT

Erythromelalgia is a rare syndrome, and there is little information about its natural history, optimal treatments, and effect on quality of life. This retrospective, review of patients seen at the Mayo Clinic attempts to address some of these gaps in our knowledge. Few large case-series have been reported. [5,9,10] A comprehensive prospective evaluation of 40 patients and a review of existing literature on erythromelalgia has recently been published.[11]

We recognize that a retrospective study of a rare, poorly defined clinical syndrome at a tertiary referral center has several limiting flaws. The study was subject to recall bias because questionnaires were used. The results may partly reflect the "Berkson bias," because patients coming to our tertiary referral center are more likely to have more than 1 medical problem, and the "survival bias," because patients at a tertiary referral center are generally seen later in the course of their disease. More than 70 physicians at our institution were involved with making the diagnosis of erythromelalgia in the patients described. A precise estimate of the number involved with diagnosis is difficult at a multi-specialty group practice because the final diagnosis is usually arrived at after multiple consultations among various specialties and subspecialties, including internal medicine, vascular medicine, dermatology, and neurology.

However, descriptive studies are necessary in rare disorders such as this and give insight unavailable in case reports. Furthermore, an understanding of erythromelalgia is important since, as we have shown, the diagnosis is associated with significantly diminished scores in almost all health domains (Table 3) and with a significant decrease in survival compared with that in age- and sex-matched control subjects (Figure 2). Three patients who committed suicide had erythromelalgia listed on their death certificates as the second cause of death (Table 1). The symptoms can be devastating for the patients.

Diagnosis was made by clinical history and was supported by abnormal findings on physical examination and raised temperature in the affected extremity when the symptoms were present. If symptoms could not be elicited, the diagnosis relied on history alone. Only about two thirds of patients had abnormal findings on physical examination. Because of the intermittent occurrence of erythromelalgia, diagnosis may have to rely on history alone. The definition of erythromelalgia used in this study was the triad of red, hot, painful extremities, which was used in the original description of the syndrome. Other authors [12,13] have proposed additional criteria for diagnosis, but these were not used since this was a retrospective study and the required additional data were variably recorded. The terms erythromelalgia and erythermalgia were used interchangeably in accord with the original term proposed by Smith and Allen from the Mayo Clinic in 1938: "This term [erythromelalgia] is not entirely adequate because it does not denote the importance of heat.... We propose . . . to substitute a more descriptive term, namely, `erythermalgia' for the syndrome commonly called `erythromelalgia'. . . ."[4, p175] We did not use the subclassification proposed by Kurzrock and Cohen,[14] which included the terms "adult-onset erythromelalgia" and "early-onset erythromelalgia." Nor did we use the subclassifications proposed by Drenth and Michiels,[15] who divided the syndrome of hot, burning extremities into entities designated as "erythromelalgia" (aspirin-responsive disease associated with thrombocytosis, related to a

myeloproliferative disorder) and "erythermalgia" (aspirin-resistant disease), erythermalgia being then subclassified into a primary form with onset at a young age and a secondary form. Thus, for this study and for clinical purposes, we were "lumpers."[3]

There is a wide differential diagnosis for that erythromelalgia includes reflex sympathetic dystrophy, angiodyskinesia, acrocyanosis, and lipodermatosclerosis.

Cutaneous ulcers and unspecified skin damage were present in many of the patients at the initial examination and in those responding to the survey. Immersion of the various body parts in cold water or ice causes a chronic cold-induced injury to the extremities. In the advanced stages of erythromelalgia, patients can appear to have severe ischemia when in reality they have a cold induced injury.

Comorbidities are listed in the "Comorbidities" subsection of the "Results" section. A history of smoking was prevalent in the patients studied. Lrythromelalgia has been reported to occur in association with drugs (verapamil,[16] nicardipine,[17] bromocriptine,[17,18] pergolide,[19] and mercury poisoning'20]), rheumatologic disease (systemic lupus erythematosus[21,22] and Raynaud syndrome[23]), other disease states (eg, pernicious anemia,[24] thrombotic thrombocytopenic purpura[25] hereditary sensory neuropathy,[26] infectious mononucleosis,[27] acute diabetic neuropathy,[28] and vasculitis[29,30]), and pregnancy.[31] In one series,[5] 30 (59%) of 51 patients, and in another [32] 9 (56%) of 16 patients, were said to have primary disease. Many authors refer to erythromelalgia in the context of these Comorbidities and associations as "secondary" erythromelalgia. We chose not to separate out patients with comorbid conditions, because we could not be sure their erythromelalgia was truly secondary to those conditions.

Myeloproliferative disease has been particularly associated with erythromelalgia in previous reports.[5,33-37] In this study, although 15 patients (8.9%) had myeloproliferative disease at the time of diagnosis of the erythromelalgia, myeloproliferative disease subsequently developed in only 2 (1.3%). This figure is lower than those suggested by previous case series (19.6%[5] and 25% [31]). There have been numerous anecdotal reports of myeloproliferative disease associated with erythromelalgia [32-36]; the myeloproliferative disease may succeed or precede the diagnosis of erythromelalgia.[5]

We did not find skin biopsy specimens to be helpful in diagnosis, because they showed nonspecif1c changes and did not confirm the thrombi and intimal proliferation reported by Crone et al [38] and Michiels et al.[39] These negative findings in 12 patients with erythromelalgia add to the literature on skin biopsy in this disorder. The literature concerning skin biopsy in erythromelalgia is extremely limited, consisting of case. reports, small case series [38,39] or reports of biopsies from patients with erythromelalgia in the context of specific disorders.[40] Case reports and small case series tend to report positive findings and neglect to report negative findings such as ours. One reason for very few pathological reports in this disorder is the fear that biopsy sites will not heal. Further studies are necessary to help delineate the pathologic features of this condition.

A detailed presentation of the vascular and neurophysiological findings will be published separately.[8] During symptoms, an increase in blood flow and temperature is accompanied paradoxically by a decrease in oxygenation of the affected area; a high proportion of patients have a distal small fiber neuropathy with selective involvement of cutaneous sympathetic fibers; in addition, large fiber neuropathy is often present.

Inherited primary erythromelalgia has previously been reported, including in a young woman and her mother [41] and a kindred of 29 persons affected with erythromelalgia in 5 generations, showing autosomal dominant inheritance.[42]

We report the outcome of disease in a large cohort of patients. We found that approximately equal proportions of patients became worse, stayed the same, or got better, and 10% experienced resolution of disease over a mean of 8.7 years. Kalgaard et al[9] also reported outcome in erythromelalgia but divided their patients into different groups. The Kaplan-Meier survival curves demonstrated a significant decrease in survival compared with age- and sex-matched control subjects (Figure 2). When observed causes of death (Table 1) were compared with expected causes of death in an age- and sex-matched US general population, rates of death from myeloproliferative disease, suicide, and connective tissue disease were over represented (95% confidence interval).

No single medication, drug group, or method of treatment was found to be universally helpful in the relief of symptoms in our patients (Table 2). The disease was not exquisitely sensitive to aspirin as described in previous reports.[5,32] Almost all patients had already tried aspirin before coming to our institution. On initial presentation, 60% of the patients reported that aspirin had provided no relief of symptoms (data not shown). Furthermore, aspirin was of no help to more than half of the patients responding to our survey. Numerous other drugs and methods of treatment were used with varying success. In total, 84 different medications and therapeutic methods were attempted by our patients; data in Table 2 show responses to only the most commonly tried treatments. Many different treatments have previously been reported to alleviate symptoms in individual patients.[43-51]

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REFERENCES

1. Mitchell SW. On a rare vaso-motor neurosis of the extremities, and on the maladies with which it may be confounded. Ain J Med Sci. 1878;76:17-36. 2. Michiels JJ. Erythromelalgia versus erythermalgia [letter]. Lancet. 1990;336: 183-184. 3. Michiels JJ, Drenth JP. Erythromelalgia and erythermalgia: lumpers and splitters. Int J Dermatol. 1994;33:412-413. 4. Smith LA, Allen EV. Erythermalgia (erythromelalgia) of extremities; a syndrome characterized by redness, heat and pain. Am Heart J.1938;16:175-188. 5. Babb RR, Alarcon-Segovia D, Fairbairn JF. Erythermalgia: review of 51 cases. Circulation. 1964;29:136-141. 6. WeirJJr,ed.SF-36 Health Survey Manual and Interpretation Guide. Boston, Mass: Health Institute, New England Medical Center; 1993. 7. McHorney CA, Ware JE Jr, Rogers W, Raczek AE, Lu JFR. The validity and relative precision of MOS short-and long-form health status scales and Dartmouth COOP charts: results from the Medical Outcomes Study. Med Care. 1992;30 (suppl):MS253-MS265. 8. Sandroni P, Davis MOP, Harper CM Jr, etal. Neurophysiologic and vascular studies in erythromelalgia: a retrospective analysis. J Clin Neuromuscular Dis. In press. 9. Mork C, Kalgaard OM, Kvernebo K. Erythromelalgia: a clinical study of 102 cases [abstract]. Australas J Dermatol. 1997;38 (suppl 2):50. 10. Kalgaard OM, Seem E,

Kvernebo K. Erythromelalgia: a clinical study of 87 cases. J Intern Med. 1997;242:191-197. 11. Kvernebo K. Erythromelalgia-a condition caused by microvascular arteriovenous shunting. Vasa.1998;27(suppl51):3-39. 12. Thompson GH, Hahn G, Rang M. Erythromelalgia. Clin Orthop.1979;144:249-254. 13. Littleford RC. Skin Microvascular Function and Its Relevance to Erythromelalgia [thesis]. Dundee, Scotland: University of Dundee; 1998. 14. Kurzrock R, Cohen PR. Erythromelalgia: review of clinical characteristics and pathophysiology. AM J Med. 1991;91:416-422. 15. Drenth JP, Michiels JJ. Erythromelalgia and erythermalgia: diagnostic differentiation. Int J Dermatol. 1994;33:393-397. 16. Drenth JP, Michiels JJ, Van Joost T, Vuzevski VD. Verapamil-induced secondary erythermalgia. Br J Dermatot. 1992;127:292-294. 17. Levesque H, Moore N, Wolfe LM, Courtois H. Erythromelalgia induced by nicardipine (inverse Raynaud's phenomenon?). BMJ.1989;298:1252-1253. 18. Eisler T, Hall RP, Kalavar KA, Canne DB. Erythromelalgia-like eruption in parkinsonian patients treated with bromocriptine. Neurology. 1981;31:1368-1370. 19. Monk BE, Parkes JD, Du Vivier A. Erythromelalgia following pergolide administration. Br J DermatoL 1984;111:97-99. 20. Martin JC, Lacombe D, Lefebvre D, Bonafe JL, Taieb A, Maleville J. Erythromelalgie: une observation familiale: discussion sur le role du mercure. Ann Dermatol Venerea1.1994;121:309-314. 21. Michiels JJ. Erythermalgia in SLE [letter]. J Rheumatol. 1991;18:481-482. 22. Drenth JP, Michiels JJ, Van Joost T, Vuzevski VD. Secondary erythermalgia in systemic lupus erythematosus. J Rheumatol. 1993;20:144-146. 23. Slutsker GE. Coexistence of Raynaud's syndrome and erythromelalgia [letter]. Lancet 1990;335:853. 24. Mehle AL, Nedorost S, Camisa C. Erythromelalgia. IntJDermato1.1990;29:567570. 25. Yosipovitch G, Krause I, Blickstein D. Erythromelalgia in a patient with thrombotic thrombocytopenic purpura. J Am Acad Dermatol. 1992;26:825-827. 26. Herskovitz S, Loh F, Berger AR, Kucherov M. Erythromelalgia: association with hereditary sensory neuropathy and response to amitriptyline. Neurology. 1993; 43:621-622. 27. Clayton C, Faden H. Erythromelalgia in a twenty-year-old with infectious mononucleosis. PediatrInfect DisJ.1993;12:101-102. 28. Vendrell J, Nubiola A, Goday A, et al. Erythromelalgia associated with acute diabetic neuropathy: an unusual condition. Diabetes Res. 1988;7:149-151. 29. Drenth JP, Michiels JJ, Van Joust T, Vuzevski VD. Erythermalgia secondary to vasculitis. Am J Med. 1993;94:549-550. 30, Ratz J, Bergfeld SF, Steck WD. Erythermalgia with vasculitis: a review. J AM Acad Dermatol. 1979;1:433-450. 31. Garrett SJ, Robinson JK. Erythromelalgia and pregnancy. Arch Dermato1.1990; 126:157-158. 32. Levesque H, Cailleux N, Courtois H. Erythromelalgia in adults: apropos of 16 cases. Rev Rheum Mal Osteoartic. 1992;59:258-263. 33. Michiels JJ, Van Genderen PJ, Van Vliet HH. Erythromelalgia and arterial thrombophilia in thrombocythemia. Ann N V Acad Sci. 1994;714:318-321. 34. Michiels JJ, ten Kate FJ. Erythromelalgia in thrombocythemia of various myeloproliferative disorders. Am J Hematol. 1992;39:131-136. 35. Kurzrock R, Cohen PR. Erythromelalgia and myeloproliferative disorders. Arch Intern Med. 1989;149:105-109. 36. Itin PH, Winkelmann RK. Cutaneous manifestations in patents with essential thrombocythemia. J Am Acad Dermatol. 1991;24:59-63. 37. Alarcon-Segovia D, Babb RR, Fairbairn JF II, Hagedorn AB. Erythermalgia: a clue to the early diagnosis of myeloproliferative disorders. Arch Intern Med. 1966; 117:511-515. 38. Croue A, Gardembas-Pain M, Verret JL, Boasson M, Rousselet VIC, Saint Andre JP. Lesions histopathologiques de I'drythromdlalgie au cours d'une thrombocytbmie

essentielle. Ann Pathol.1993;13:128-130. 39. MichielsJJ,AbelsJ,SteketeeJ,vanVIietHH,VuzevskiVD.Erythromelalgiacaused by platelet-mediated arteriolar inflammation and thrombosis in thrombocythemia. Ann Intern Med. 1985;102:466-471. 40. Michiels JJ, ten Kate FW, Vuzevski VD, Abels J. Histopathology of erythromelalgia in thrombocythaema. Histopathology. 1984;8:669-678. 41. Michiels JJ, Van Joost T, Vuzevski VD. Idiopathic erythermalgia: a congenital disorder. J Am Acad Dermatol. 1989;21:1128-1130. 42. Finley WH, LindseyJR Jr, Fine JD, Dixon GA, Burbank MK. Autosomal dominant erythromelalgia. Am J Med Genet. 1992;42:310-315. 43. Calderone DC, Finzi E. Treatment of primary erythromelalgia with piroxicam. JAM Acad Dermatol.1991;24:145-146. 44. Muhiddin KA, Gallen IW, Harries S, Pearce VR. The use of capsaicin cream in a case of erythromelalgia. Postgrad Med J. 1994;70:841-843. 45. Mohr M, Schneider K, Grosche M, Hildebrandt J. Cervical epidural infusion of morphine and bupivacaine in severe erythromelalgia. Anasthesiol Intensimed Notfallmed Schmerzther. 1994;29:371-374. 46. Graziotti P, Gouche C. Control of intractable pain in erythromelalgia by using spinal cord stimulation. J Pain Symptom Manage. 1993;8:502-504. 47. Chakravarty K, Pharoah POP, Scott DGI, Barker S. Erythromelalgia-the role of hypnotherapy. Postgrad Mod J. 1992;68:44-46. 48. Ozsoylu S, Caner H, Gokalp A. Successful treatment of erythromelalgia with sodium nitroprusside. J Pediatr.1979;94:619-621. 49. Ozsoylu S, Coskun T. Sodium nitroprusside treatment in erythromelalgia. Eurd Pediatr. 1984;141:185-187. 50. Pepper H. Primary erythermalgia: report of a patient treated with methysergide maleate. JAMA. 1968;203:1066-1067. 51. Kandel El. Stereotactic surgery of erythromelalgia. Stereotact Funct Neurosurg. 1990;5455:96-100.