- Case: Treating Primary Erythromelalgia with Ibuprofen
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Resolution of Primary Erythromelalgia Following Ibuprofen

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Erythromelalgia presents with recurrent and symmetric burning pain, heat, and erythema of the extremities. The feet (88 percent), hands (26 percent), and legs (14 percent) are most frequently implicated; other sites include the ears, neck, and face.[1] Attacks are typically intermittent (97 percent) and may last from minutes to days.[1] Symptoms are pathognomonically exacerbated by heat (51 percent) and exercise (29 percent) and alleviated by cold water and/or ice (67 percent).[1]

Primary erythromelalgia (PEM) may be sporadic or familial and is diagnosed after eliminating causes of secondary erythromelalgia (SEM). Though patients with inherited PEM are typically young children, erythromelalgia remains more common in adults (average age 56 to 65 years).[1,2] In a study of 168 patients, only three patients (two percent) were younger than 12.[1]

Supportive therapy includes rest, elevation, removing shoes and/or gloves, and cooling.[3] While SEM is typically treated by addressing the underlying cause, there is no first-line treatment for PEM. In a review of 168 patients, Davis, et al. noted the utilization of 84 different medications.[1]

Herein we report a case of PEM in a six-year-old girl in remission following ibuprofen use and review the diagnosis, pathogenesis, treatment, and prognosis of pediatric PEM reported in the literature.

CASE REPORT

A six-year-old girl with a past medical history significant for asthma, eczema, and allergic rhinitis presented with erythema, burning pain, and warmth of the bilateral ulnar palms, occurring intermittently for months at the same location with no known inciting factor (Figure 1). Symptoms were exacerbated by warm water and weather and alleviated with cold compresses and ice. The patient also licked her hands several times daily to alleviate symptoms. The patient's mother denied hyperhidrosis, joint pain, or fever in the child.

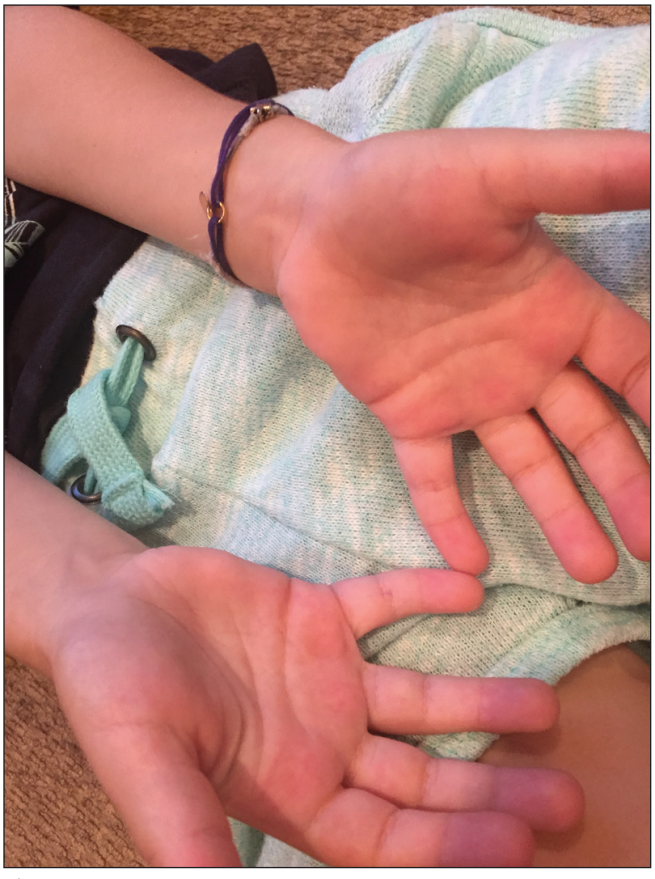

Figure 1

The patient's history was significant for a several-year history of occasional eczema flare-ups on the flexural surfaces and, most commonly, the hands managed with Cetaphil body wash and a combination of Trixera wash, triamcinolone

TABLE 1. WORK-UP TO ELIMINATE SECONDARY CAUSES			
CBC	**Lipid panel**	**SS-A and SS-B**	**HLA-B27**
CMP	Uric acid	Antinuclear antibodies	Immunoglobulins
Vitamins B6 and B12	Thyroid panel	Rheumatoid factor	Gamma glutamyl transferase
Vitamin E	Hep A, B, C titers	Hu, Ri, and Yo Ab	Complement C-3 and C-4
Folate	HIV 1,2 Ag/Ab Combo	Neuronal nuc Ab	C-reactive protein
Hemoglobin electrophoresis	Syphilis IgG, RPR	Amphiphysin Ab	ESR

cream 0.1%, and cetirizine or hydroxyzine for flare-ups. In addition, nine months prior to her current presentation, the patient presented with large bullae and several smaller bullae on her palms. There was no pain, burning, warmth or pruritus at that time. The patient was diagnosed with dyshidrotic eczema and was treated with clobetasol ointment 0.05% and mupirocin ointment, and the bullae resolved within a week.

Current physical exam was significant for xerotic, erythematous, palms that were warm to the touch. There were no bullae present. During the office visit, the patient wanted to hold an ice pack or popsicle. She also complained of hand discomfort upon palpation. Her motor and sensation of her distal upper extremities were intact. Vital signs were normal and the remainder of her physical exam was unremarkable.

Diagnosis of PEM was made for her current presentation based on the patient's history and physical exam findings and after an extensive work-up that eliminated secondary causes (Table 1). In addition, her previous treatment for dyshidrotic eczema including the topical steroid and mupriocin did not improve her symptoms, further supporting PEM. On laboratory testing, eosinophils and lymphocyte percentage were slightly elevated (EO# [0.52, normal 0.00-0.39], LY% [46, normal 25-45]), likely due to a recent asthma exacerbation and URI. Genetic testing for mutations in the sodium channel Na(v)1.7 was not performed. Family history was significant for asthma and childhood eczema, but not for erythromelalgia.

Fans, wet dressings, ice, and elevation of the affected extremities to alleviate pain and avoidance of hot environments to minimize attack frequency were advised. Recently, she had a febrile URI and mild asthma exacerbation for which ibuprofen was used infrequently for two weeks. During these two weeks, the patient's burning and pain resolved. It is possible that oral ibuprofen reduced her hand discomfort. The patient has not complained of significant hand pain on four-month follow-up.

DISCUSSION

Diagnosis of erythromelalgia is clinical, as there is no confirmatory diagnostic test. Histologic findings are non-specific.[4] Our patient met the diagnostic criteria for PEM: episodic bilateral burning pain, warmth, and erythema of the upper or lower extremities, exacerbation by pressure, heat, and/or exercise, alleviation by elevation and/

TABLE 2. CAUSES OF SECONDARY ERYTHROMELALGIA	
Drugs	Calcium channel blockers (verapamil,[7,8] nicardipine,[9] nifedipine,[10] ciclosporin[11]) ergot-derivative dopamine agonists (bromocriptine,[12,13] pergolide[14]), statins,[15] norephedrine,[16] ticlopidine,[17] SSRIs (sertraline, fluoxetine)[18,19]
Immunologic disease	Systemic lupus erythematosus,[20-22] pernicious anemia,[23] idiopathic and thrombotic thrombocytopenic purpura,[24,25] vasculitis,[26] rheumatoid arthritis,[27] multiple sclerosis[28-30]
Toxins	Clitocybe amoenolens mushroom,[31] mercury,[32,33] iodide contrast[27]
High stress	Post-operative,[34] pregnancy,[35] back/neck trauma[27]
Malignancy	Essential thrombocythemia and polycythemia vera,[36-39] leukemia (especially CML),[6,40] paraneoplastic syndrome,[41,42] myelodysplastic disorder,[43] malignant thymoma,[44] astrocytoma[45]
Vaccines, infectious disease	Influenza vaccine,[46,47] hepatitis B vaccine,[48] mononucleosis,[49] human immunodeficiency virus,[50] leprosy,[51] pox virus[52]
Neuromuscular	Hereditary sensory neuropathy,[53] diabetic neuropathy,[54] peripheral neuropathy,[55,56] neurofibromatosis,[57] sciatica/spinal cord disease,[27] carpal tunnel syndrome[27]
Other conditions	Hereditary spherocytosis,[27] gout,[27,58] frostbite,[27] conversion disorder[27]
Cardiovascular	Atherosclerosis,[27] hypertension,[59,60] venous insufficiency,[29] diabetes (types 1 and 2),[54] hypercholesterolemia[27]

TABLE 3. TREATMENT RESULTING IN IMPROVEMENT IN PEDIATRIC ERYTHROMELALGIA

Treatment (total # treated)	Results
Topical lidocaine patches (14)	5 marked improvement (36 percent); 1 no improvement (7 percent); 8 lost to follow-up
Aspirin (8)	2 marked improvement (25 percent); 1 some improvement (13 percent); 1 no improvement; 4 lost to follow-up
Topical gel 1% amitriptyline and 0.5% ketamine (5)	1 marked improvement (20 percent); 1 no improvement (20 percent); 3 lost to follow-up
Amitriptyline or nortriptyline (4)	2 marked improvement (50 percent); 1 no improvement (25 percent); 1 lost to follow-up
Carbamazepine, phenoxybenzamine, fluphenazine, epidural block (1 each)	1 marked improvement (100 percent)
Diazepam, propranolol, plasma exchange, biofeedback (1 each)	1 some improvement (100 percent)

or cold, and refractoriness to treatment.[5] Due to PEM's intermittent nature, patients may not present with findings on physical exam (33 percent); in these cases, diagnosis depends on history.[1] When present, physical findings include: erythema (49 percent); acrocyanosis (10 percent); ulceration (six percent); or a reticular vascular pattern (five percent).[1]

Underlying causes of SEM must be eliminated (Table 2). Patients diagnosed with PEM should still be monitored by CBC to assess for myeloproliferative disorder, which, when present, follows erythromelalgia onset by a median 2.5 years.[6]

Differential diagnoses include: Raynaud's syndrome; complex regional pain syndrome; systemic lupus erythematosus; scleroderma; juvenile rheumatoid arthritis; dermatomyositis; hypothyroidism; Fabry disease; angiodyskinesia; cellulitis; and erysipelas.

Most patients experience decreased quality of life. Extreme discomfort often results in decreased physical activity (66 percent) and in patients taking drastic measures to alleviate discomfort, such as walking barefoot and elevating and soaking the extremities (some more than 20 hours daily). Truancy (34 percent) and other behavioral problems (28 percent) are common. On an average nine-year follow-up of 15 pediatric patients, five had stable disease (33 percent), four had improvement (27 percent), two had resolution (13 percent), one had worsening disease (seven percent), and three had died (20 percent). Mortality may result from suicide, sepsis from prolonged soaking, and treatment-related bone-marrow failure.[61] Cutaneous complications include: skin maceration due to ice and/or cold water (22 percent); infection (16 percent); ulceration (13 percent); and gangrene (one percent).[1]

The incidence of erythromelalgia is between 0.36 to 1.3/100,00062 and more commonly affects females (3:1).[1,2] PEM comprises 66 percent of cases.[27]

Familial PEM is inherited as an autosomal dominant[63-65] mutation in SCN9A, a gene on chromosome 2q66 that encodes the alpha-subunit of Na(v)1.7 voltage-gated sodium channels.[67] Mutations in Na(v)1.7, expressed by neurons involved in nociception and sympathetic outflow, render the former hyperexcitable and the latter hypoexcitable,[68] thus contributing to increased cutaneous blood flow resulting in pain, warmth, and erythema.[69] Alternatively, abnormal cutaneous blood flow in patients with wild-type Na(v)1.7 may be explained by the shunting hypothesis, which proposes that in erythromelalgia, cutaneous flow is not evenly distributed. Specifically, it is reduced secondary to bypassed capillaries in some areas and increased in others secondary to hypoxia-induced vasodilation.[70] Pathogenesis has been attributed to endothelial dysfunction and consequent reduction in endothelial-derived nitric oxide, resulting in hypertension and vasoconstriction-induced hypoxia followed by reactive hyperemia.[71] Kalgaard, et al. proposed that erythromelalgia be considered a common vascular response provoked by diverse factors, i.e. infectious, traumatic, immunologic, carcinogenic, etc.[27] The multitude of factors contributing to disease pathogenesis explains the lack of universal success of a single treatment.

Inflammation is also central to disease pathogenesis.[72] In addition to the inflammatory infiltrate observed histologically,[4] the presenting features of erythromelalgia, especially heat, pain, and erythema, are among the cardinal signs of inflammation. Erythromelalgia has not been reported to present with vesicles unless as sequelae to excessive cold therapy and/or infection.[73,74,75] Accordingly, the bullae observed in our patient were likely due to her recurring dyshidrotic eczema, also an inflammatory disease, but without erythema.[76,77] The patient's chronic inflammatory state due to her recurring asthma, eczema, and allergic rhinitis might have predisposed her to developing erythromelalgia.

In a retrospective analysis of 32 pediatric patients (mean age 14, range five to 18), Cook-Norris, et al. reported on the efficacy of various therapies with different mechanisms of

action (Table 3). Topical lidocaine as the most commonly prescribed treatment.[61] Other treatments in pediatric patients reported in the literature include combination of IV lidocaine and oral mexiletine,[78] oral mexiletine alone,[79] sodium nitroprusside,[59,80] recombinant growth hormone,[81] regional anesthesia blockade,[82] thalamic stimulation,[83] gabapentin,[84,85] cetirizine,[86] and steroids.[87]

Genetic testing for specific mutations in Na(v)1.7 is helpful in guiding treatment. Specifically, patients' response to treatment with the sodium channel blockers lidocaine, mexiletine, and carbamazepine is limited in patients with wild-type Na(v)1.7 and treatment response varies depending on the specific mutation.[73,88,89]

Other treatments that target abnormal cutaneous blood flow and/or inflammation are helpful in treatment refractory patients and/or those with wild-type Na(v)1.7. Effective treatments regulating blood flow include: sodium nitroprusside;[80] iloprost;[90] misoprostol;[91] and NSAIDs.[61,92] Effective medications targeting inflammation include: prostaglandins;[90,91] NSAIDs;[61,92] and steroids.[93]

CONCLUSION

We report on a rare case of PEM in a six-year-old girl with a past medical history significant for asthma, eczema, and allergic rhinitis. Currently, our patient is not complaining of significant hand pain, which may be due to ibuprofen use for an URI. Accordingly, ibuprofen may be particularly helpful in treating erythromelalgia patients with a history of other inflammatory conditions, such as our patient, and this case adds to the case reports that have demonstrated the success of NSAIDs in treating pediatric erythromelalgia. ■

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Fire Power: Sometimes You Need to Let Employees Go

In the latest edition of *Practice Path MD*, Lisa Waite explains how and why to fire staffers who just don't fit. Read the full story online: practicepathmd.com/articles/julaug-2017/

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"The true definition of leadership reminds us that leadership can be messy and even scary, but a leader is called to manage the workforce to success. In part, you can't retain the one in risk of sacrificing the many. You must sacrifice the one to maintain the culture and 'civilization.' I once heard a conference speaker, express. 'It must be one for all, never all for one.' Drucker reinforces this, 'Letting the wrong people hang around is unfair to all the right people, as they inevitably find themselves compensating for other's ineffectiveness.'

You can't shy away from these hard calls. One client of a national snack food organization recently remarked that "releasing" people remains his biggest leadership challenge. I noted that a benchmark of his leadership in these circumstances is not having to remove people but more importantly his willingness to do so. I suggested that his concern about what others think about his leadership effectiveness will only worsen with indecision and hesitancy. Keeping poor performers is unfair to all the great performers who pick up the slack."

—Lisa Waite

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