Annals of Case Reports & Reviews

Case Report

doi: 10.39127/2574-5747/ACRR:1000391
Harmel A, et al. (2024) Annal Cas Rep Rev: ACRR-391

Unusual Pattern of Lower Extremity Discoloration in a Pediatric Patient: Erythromelalgia

Allison Harmel, MD[3], Maria Kelly, MD[1], Diane Howell, MD[1], Leandra Woolnough, MD[2], Molly Posa, MD[1*]

[1]University of Florida, Department of Pediatrics
[2]University of Florida, Department of Pediatric Rheumatology/Immunology
[3]University of North Carolina, Department of Ophthalmology

***Corresponding author:** Molly Posa, MD, University of Florida, Department of Pediatrics. Email: mollyposa@ufl.edu; Co-author(s): mnkelly@ufl.edu (MK); dharrell@ufl.edu (DH); l.wollnough@ufl.edu (LW); Allison_harmell@med.unc.edu (AH)

Citation: Harmel A, Kelly M, Howell D, Woolnough L, Posa M (2024) Unusual Pattern of Lower Extremity Discoloration in a Pediatric Patient: Erythromelalgia. Annal Cas Rep Rev: ACRR-391.

Received Date: 10 May, 2024; **Accepted Date:** 24 May, 2024; **Published Date:** 03 June, 2024

Abstract

This manuscript presents a case of erythromelalgia in a 17-year-old female, discussing the challenges in diagnosis, clinical presentation, differential diagnoses, and management strategies for this rare but potentially serious condition characterized by extremity color changes and pain.

Keywords: *pediatric, erythromelalgia, rheumatology, dermatology.*

Pediatric providers are challenged to identify a multitude of color changes in children's hands and feet. The etiology of discoloration can vary from benign findings such as acrocyanosis to more complex etiologies such as Raynaud's phenomenon, connective tissue diseases, and systemic lupus. This case discusses erythromelalgia, a rare but potentially serious disease associated with color changes in the extremities. Erythromelalgia causes erythema and pain, typically characterized as burning or itching. A case of erythromelalgia in a 17-year-old female who presented with lower extremity burning and erythema is described.

Case Presentation

A 17-year-old female presented to a pediatric clinic for routine supervision of her attention deficit hyperactivity disorder (ADHD). Her ADHD had been well controlled with long-acting amphetamine-dextroamphetamine at a stable dose for the past two years. During the visit, she stated she had experienced episodic cold sensations and blue discoloration of her feet for the past four months. These episodes occurred when she did not have shoes or socks on. The events happened one to two times daily and lasted up to 60 minutes before self-resolving. The bluish discoloration was bilateral, although worse on her right foot, and was concentrated circumferentially on her distal feet.

Additionally, the patient stated that her feet, right more than left, would intermittently become erythematous; this discoloration would self-resolve within an hour (Figure 1). She noticed these episodes tended to occur when her feet would get warm or after a hot shower. She denied loss of sensation during these episodes but did note burning sensations with erythematous foot discoloration. Bluish and erythematous discoloration episodes did not occur concurrently and had separate triggers. Discoloration never spread past her ankles and circumferentially involved the entirety of her feet and toes. Since the episodes self-resolved within an hour, the parents and patient had not sought treatment.

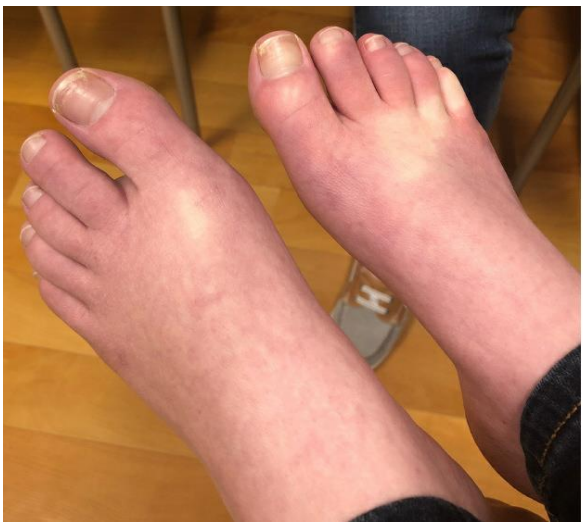

Figure 1: A photo taken in the pediatric clinic upon the patient's initial presentation. Here you can see the bilateral red discoloration along with the blanching of the right foot after pressure via palpation was applied. A few seconds after palpation, the color returned to its original shade.

Physical Exam

On physical exam, her feet had a confluent bluish discoloration bilaterally, right greater than left, equally distributed from the tips of the toes to her ankles. Her feet were cold to touch, but she had 1+ pulses at the posterior tibial and dorsalis pedis sites. Pressure applied to her feet caused blanching of the discoloration, followed by a brisk shift to erythema after a few seconds (Figure 2). No color changes were noted on her hands. The remainder of the physical examination, including vital signs, was normal.

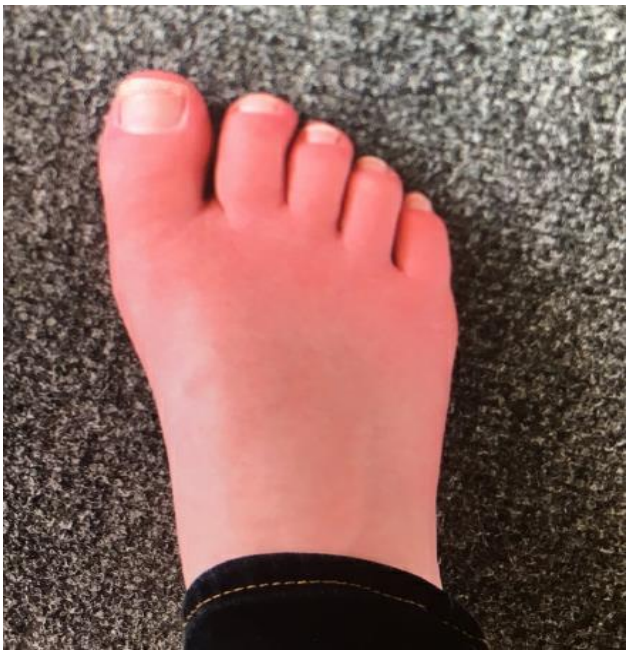

Figure 2: A photo taken by the patient at home representing an episode of an acute flare. This flare was characterized by bilateral redness and swelling in her feet, worse on the right than the left. This episode resolved spontaneously without treatment.

Differential Diagnoses

Due to the color change pattern in the feet following a triphasic pattern, the leading concern was Raynaud's phenomenon (RP). Other differentials included systemic lupus, connective tissue disease, and vasculitis. A panel of labs, including a complete blood count, comprehensive metabolic panel, urinalysis, antinuclear antibody (ANA), thyroid stimulating hormone, c-reactive protein, and erythrocyte sedimentation rate, were ordered to further evaluate for inflammatory, autoimmune, and rheumatologic causes. Results were unremarkable except for a low-titer positive ANA titer (1:40) with nucleolar pattern distribution. Due to a concern for RP and a positive ANA titer, the patient was referred to a pediatric rheumatologist.

Erythromelalgia Diagnosis

The rheumatologist identified a pattern of episodes of bilateral foot erythema triggered by heat exposure. A history of Crohn's disease in the maternal grandfather was noted. Their clinical evaluation revealed a well-appearing young woman with mild diffuse erythema and mottling that was not well demarcated, present bilaterally on her feet (right greater than left). No digital ulcerations, malar rashes, sclerodactyly, or purpura were identified. Since the patient had a low-titer positive ANA, a reassuring clinical exam, and no other evidence of systemic inflammation on laboratory studies, rheumatology felt systemic lupus, vasculitis, and underlying connective tissue disease were unlikely. Of note, stimulants can cause vascular disorders, including RP, and the medication the patient is taking (amphetamine-dextroamphetamine) has this potential side effect. However, the patient had been stable on this medication regimen for two years before the noted symptoms. Additionally, the distribution of her symptoms throughout the entire foot, without clear demarcation, contrasted with the typical pattern of a well-demarcated digitally focused distribution classically found in RP. Due to the pattern of distribution, the accompanied intermittent burning, and the trigger by heat, the patient was diagnosed by rheumatology with erythromelalgia.

Discussion

Erythromelalgia is characterized by episodes of a bluish-red discoloration localized to the extremities, more frequently in the lower extremities and most often bilateral in distribution [1]. The word erythromelalgia can be broken down into the Greek words "erythros" (red), "melos" (extremity), and "algos" (pain), which fits the description of the clinical picture of this disorder. The incidence of the primary form of erythromelalgia ranges from 0.36 to 1.1 per 100,000 persons [1]. The redness is associated with warmth of the extremities and a perception of pain often described as burning and pruritic. The episodes last from minutes to hours, and the frequency of symptoms ranges from daily to as infrequent as a few episodes yearly [1]. The frequency of the symptoms can often be attributed to exacerbating factors and can be precipitated by physical activity, prolonged standing, or heat [2]. The flares tend to present later in the day and progress into the evening, often resulting in sleeping difficulties due to the burning sensation [3].

Erythromelalgia is generally categorized into two separate etiologies: primary and secondary. Primary disease is typically diagnosed in the first two decades of life, while secondary disease has a mean onset of 49.1 years [2]. Primary disease is caused by an autosomal dominant mutation in the SCN9A gene [4]. This gain of function mutation affects a gene that codes for a voltage-gated sodium channel expressed on small nociceptive neurons, making the channels easily excitable. This is thought to play a crucial role in the etiology of pain episodes [5]. Secondary erythromelalgia has a less clear etiology but is known to be associated with medications, connective tissue disorders, neoplasia, myeloproliferative disorders, vascular insufficiency, and autoimmune etiologies, amongst other diagnoses. Medication triggers include verapamil, nicardipine, and bromocriptine [6]. When due to hematologic disorders, pathogenesis is associated with arteriole changes leading to platelet activation. The activation of platelets in the small vessels activates prostaglandins, releasing platelet-derived growth factors, which leads to the formation of occlusive thrombi in the arterioles. Due to the pathogenic activation of platelets, this etiology of erythromelalgia can be managed with cyclooxygenase inhibitors, such as aspirin or ibuprofen, which inhibit platelet activation [7].

There are no objective diagnostic criteria for erythromelalgia, and the diagnosis is based on clinical findings [3]. The erratic nature of the disease, along with the lack of objective diagnostic criteria, often creates a diagnostic challenge for clinicians. Since patients are primarily asymptomatic, photographs of episodes or flares can be helpful in diagnosis. Providers are encouraged to follow the clinical criteria set by Thompson et al. (1979) [8]: (1) burning pain in extremities, (2) pain decreased by cooling, (3) pain increased by warming, (4) erythema of the affected skin region and (5) increase in temperature of affected skin. Although there have been cases where a skin biopsy has been used to differentiate between primary and secondary disease, generally, it is not recommended as the histopathologic changes are usually nonspecific [9].

A thorough history is essential when patients present with isolated intermittent diffuse circumferential color changes in extremities. Important factors to elicit include triggers of color change, associated pain, initial onset of symptoms, and any associated systemic findings. Acrocyanosis presents with diffuse hand and foot color changes that are usually described as blue in nature, contrasted to the red discoloration found in erythromelalgia. In addition, the color changes of acrocyanosis are usually relieved with limb elevation or warming. Furthermore, acrocyanosis is typically not painful and is associated with hand or foot hyperhidrosis. RP is a vasospastic disorder of the peripheral vasculature of extremities characterized by phasic episodic color changes from blue to white to red. It represents constricted blood flow (cyanosis), tissue ischemia (white), then recovery and reperfusion (red). RP most often affects the hands, starting on one finger and spreading symmetrically in both hands [10]. RP is classically triggered by temperature change but can also be exacerbated by stress or stimulants used to treat ADHD [11]. It also has a clear demarcation of affected tissue versus non-affected tissues, contrasting the more diffuse distribution in erythromelalgia and acrocyanosis.

Treatment of erythromelalgia is currently limited, as no single therapy has been found to be effective. The general recommendation is to approach the treatment stepwise, with the first step being anticipatory guidance to avoid situations, environments, and medications that may trigger an episode [7]. Patients should first be encouraged to keep a log of their symptoms to try and identify their triggers and, whenever possible, discontinue those triggers. Patients can pursue non-pharmacologic treatments such as elevating the affected extremity and briefly cooling the extremity in cool water or with a fan (e.g., 5 to 10 minutes every one to two hours). However, it should be emphasized that patients should not overcool the extremities by prolonged use of cooling techniques or iced water, as reports of ulcerative damage from overcooling have been noted [12].

If trigger avoidance is unsuccessful in controlling symptoms, pharmacologic agents can be utilized, including vascular agents, antidepressants, sodium channel blockers, anticonvulsants, antihistamines, topical medications, and immunosuppressants. Due to the lack of a universally accepted therapy, the etiology of erythromelalgia should be considered before trialing medications to best target the cause and symptoms and limit side effects caused by polypharmacy [7]. Patients with inherited or primary erythromelalgia caused by genetic alterations of the sodium channels on neurons should have a sodium channel blocker such as lidocaine or mexiletine or the anticonvulsant carbamazepine prescribed. Genomic analysis to evaluate the specific mutation may guide which sodium channel modulator to use, as differing studies have identified varying responses to medications dependent on which mutation was present [5].

If the patient's erythromelalgia has an unknown etiology, treatment is often a multimodal model approach of trial and error, starting with the medications with the lowest side effect profile. Aspirin is often the first-line treatment in adult patients with secondary or unknown erythromelalgia etiologies. However, the use of aspirin in pediatric patients is not recommended due to the risk of Reye syndrome [13]. After exhausting trials of other oral pharmacotherapy options, more invasive treatment may be indicated. A recent case series reported the successful use of a novel treatment of computed tomography (CT) guided lumbar sympathetic blockade for a pediatric patient refractory to other treatment modalities [14]. Although many existing and novel treatments are being studied, no single treatment is prevailing as the most beneficial. For this reason, each patient and clinician team should tailor the treatment to the patient's lifestyle and their individual response to various pharmacologic and nonpharmacologic therapies [7].

Conclusion

The patient has been followed for four years since her initial diagnosis. She is seen every three months as a component of her ADHD stimulant management, at which time her erythromelalgia is concurrently evaluated. She continues to have symptoms, but they have become milder and less frequent over the years. It is suspected that this improvement is due to trigger avoidance and a less consistent need for ADHD stimulant medication.

Acknowledgement: We have no acknowledgements to report.

Authors contribution: Each author contributed to the conceptualization, writing, and reviewing of the manuscript.

Source of funding if the project was funded: We have no funding to report.

References

1. Tang, Z., Chen, Z., Tang, B., & Jiang, H. (2015). Primary erythromelalgia: A review. *Orphanet Journal of Rare Diseases*, *10*(1), 127. https://doi.org/10.1186/s13023-015-0347-1.
2. Jha, S. K., Karna, B., & Goodman, M. B. (2021). Erythromelalgia. In *StatPearls*. StatPearls Publishing.
3. Mørk, C., & Kvernebo, K. (2000). Erythromelalgia--a mysterious condition? *Archives of Dermatology*, *136*(3), 406–409. https://doi.org/10.1001/archderm.136.3.406

4. Yang, Y. (2004). Mutations in SCN9A, encoding a sodium channel alpha subunit, in patients with primary erythermalgia. *Journal of Medical Genetics*, *41*(3), 171–174. https://doi.org/10.1136/jmg.2003.012153
5. Arthur, L., Keen, K., Verriotis, M., Peters, J., Kelly, A., Howard, R. F., Dib-Hajj, S. D., Waxman, S. G., & Walker, S. M. (2019). Pediatric Erythromelalgia and SCN9A Mutations: Systematic Review and Single-Center Case Series. *The Journal of Pediatrics, 206*, 217–224.e9. https://doi.org/10.1016/j.jpeds.2018.10.024
6. Mann, N., King, T., & Murphy, R. (2019). Review of primary and secondary erythromelalgia. *Clinical and Experimental Dermatology*, *44*(5), 477–482. https://doi.org/10.1111/ced.13891
7. Tham, S. W., & Giles, M. (2018). Current pain management strategies for patients with erythromelalgia: a critical review. *Journal of Pain Research*, 11, 1689–1698. https://doi.org/10.2147/JPR.S154462
8. Thompson, G. H., Hahn, G., & Rang, M. (1979). Erythromelalgia. *Clinical Orthopaedics and Related Research*, (144), 249–254. https://doi.org/10.1097/00003086-197910000-00042
9. Davis, M. D. P., Weenig, R. H., Genebriera, J., Wendelschafer-Crabb, G., Kennedy, W. R., & Sandroni, P. (2006). Histopathologic findings in primary erythromelalgia are nonspecific: Special studies show a decrease in small nerve fiber density. *Journal of the American Academy of Dermatology*, *55*(3), 519–522. https://doi.org/10.1016/j.jaad.2006.04.067
10. Wigley, F. M. (2002). Raynaud's phenomenon. *New England Journal of Medicine*, *347*(13), 1001–1008. https://doi.org/10.1056/NEJMcp013013
11. Laboe, C., Batchelder, E., & Vasireddy, D. (2021). Persistent Raynaud's Phenomenon Following Methylphenidate Hydrochloride Use During the COVID-19 Pandemic. *Cureus*, 13(9). https://doi.org/10.779/cureus.17647
12. Davis, M. D. P. (2013). Immersion foot associated with the overuse of ice, cold water, and fans: A distinctive clinical presentation complicating the syndrome of erythromelalgia. *Journal of the American Academy of Dermatology*, *69*(1), 169–171. https://doi.org/10.1016/j.jaad.2013.02.021
13. Chapman, J., & Arnold, J. K. (2023). Reye Syndrome. In *StatPearls (Internet)*. StatPearls Publishing.
14. Kundu, A., Rafiq, M., Warren, P. S., & Tobias, J. D. (2016). Erythromelalgia in the pediatric patient: role of computed-tomography-guided lumbar sympathetic blockade. *Journal of Pain Research*, 9, 837–845. https://doi.org/10.2147/JPR.S110688
15. Goldman, W., Seltzer, R., & Reuman, P. (2008). Association between treatment with central nervous system stimulants and Raynaud's syndrome in children: A retrospective case-control study of rheumatology patients. *Arthritis & Rheumatism*, *58*(2), 563–566. https://doi.org/10.1002/art.23301