Volume 23 Number 4 | April 2017
DOJ 23 (4): 8

Erythromelalgia involving the face

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Abstract

Erythromelalgia is a rare disorder characterized by burning pain, erythema, and increased temperature typically involving the distal extremities. Although it can progress to involve the face, erythromelalgia presenting only on the face is particularly rare. This disorder is often misdiagnosed when it presents on the extremities and is even more likely to be misdiagnosed when presenting only on the face, delaying appropriate treatment and causing considerable frustration for the patient. We report a case of a 26-year-old woman with erythromelalgia that involved only the face for a number of years and was treated unsuccessfully as rosacea, seborrheic dermatitis, and contact dermatitis. She subsequently developed involvement of the ears and hands in the more typical distribution of erythromelalgia. We discuss the differential diagnosis of erythromelalgia involving the face and extremities, the proposed pathogenesis and management of the disorder, and the psychological distress this condition can cause. Even when the correct diagnosis of erythromelalgia is made, treatment is difficult, with no single therapy consistently effective.

Keywords: erythromelalgia, erythema, rosacea

Introduction

The term "erythromelalgia" was first used by Mitchell in 1878 to describe a rare episodic condition characterized by redness (erythros) affecting the extremities (melos) and causing pain (algos) [1]. Erythromelalgia can present with lesions and symptoms only involving the face. This atypical presentation may lead to misdiagnosis and delay appropriate management. Erythromelalgia frequently follows a chronic course and is often associated with serious morbidity and mortality.

Case Synopsis

A 26-year-old otherwise healthy woman, previously seen by two other dermatologists, presented with a recurrent, intermittent, throbbing painful rash lasting for one to two hours on the face for years. Her work as a teacher involved teaching young children and

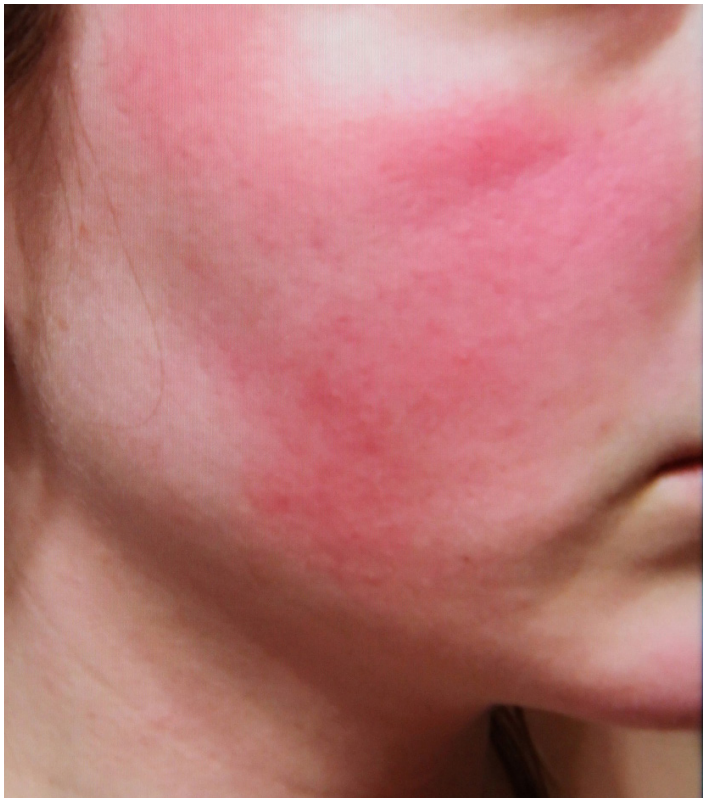

Figure 1. *Erythematous patches on the cheeks from a photograph the patient had taken during an episode.*

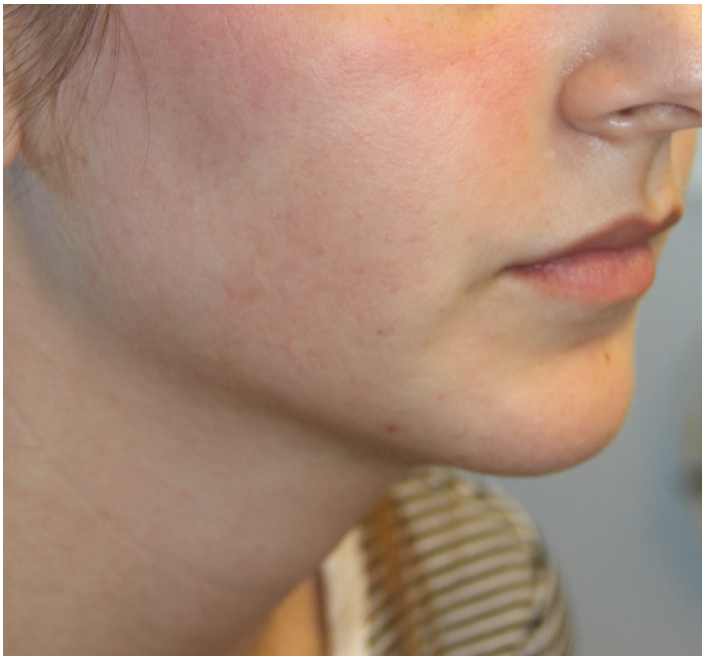

Figure 2. *Appearance on the day of one of our visits.*

the episodic marked facial erythema was a cause of great embarrassment. As a young single person, this condition also affected her social interactions. The dermatologists she had seen previously considered the diagnoses of rosacea, seborrheic dermatitis, contact dermatitis, and dry-flushing. She had been treated unsuccessfully with a multitude of topical and oral agents, including topical corticosteroids, corticosteroid-sparing agents, and both topical and oral therapies for rosacea. More recently, the rash progressed to involve her ears and hands, and she noticed that the eruption was often triggered by anxiety, emotional stress, and heat, and was alleviated by cooling herself with fans.

Examination during one of her visits revealed faint erythema of the cheeks and temples bilaterally (**Figure 2**). However, photographs from one of our patient's attacks revealed prominent, well-demarcated, erythematous patches on the cheeks (**Figure 1**), as well as the distal dorsal aspect and entire volar aspect of the hands (**Figure 3**). Previous patch testing was positive for methyl methacrylate and abitol. With the exception of a mildly elevated, homogenous pattern antinuclear antibodies (ANA), all laboratory testing, including basic laboratory studies, complement studies, and studies for connective tissue disease, were negative or normal.

Based on the clinical and laboratory data, she was diagnosed with erythromelalgia and was started on aspirin 325 mg daily with little relief. Within one week of increasing the aspirin dose to 325 mg twice daily, she reported considerable improvement. Despite continuing this dose, her lesions and symptoms relapsed. The patient was then started on propranolol 10 mg twice daily and amitriptyline 20 mg in the evening, with topical 1% amitriptyline and 0.5% ketamine compounded in a pluronic lecithin organogel as needed. She has seen improvement

Figure 3. *Erythematous patches on the distal dorsal hands and entire surface of the palm but affecting the distal aspect the most.*

with this regimen. She is also considering beginning venlafaxine for further alleviation of her symptoms.

Case Discussion

As defined by Thompson in 1979, the diagnostic criteria for erythromelalgia include burning pain of the extremities that is aggravated by warming and relieved by cooling, with erythema and increased temperature of affected skin [2]. The most frequently affected areas of the body are the feet, with reported involvement in 90% to 100% of patients in the referenced series, followed by the hands in 25% to 60%. The head and neck are affected least often in 2% to 15% [3-7]. However, a PubMed search produced only four reported cases with facial involvement and sparing of the extremities [8-11].

Erythromelalgia is classically divided into three types. Types 1 and 3 result secondarily from underlying disease, whereas type 2 describes primary, or idiopathic, erythromelalgia. Type 1, which is associated with thrombocythemia, typically occurs in adulthood and is most often unilateral. In contrast, type 2, the primary form, often appears during childhood, may be hereditary, and is more commonly bilateral. Type 3 is associated with all other underlying disorders except thrombocythemia [3]. Erythromelalgia affects females 2 to 3 times more often than males.

Although the pathogenesis of erythromelalgia is incompletely understood, the primary familial form of the disease has been associated with a gain-of-function mutation in SCN9A, encoding voltage-gated sodium channels in sensory neurons. Of note, a gain-of-function mutation in this gene has also been associated with the dominantly inherited paroxysmal extreme pain disorder, whereas a loss-of-function mutation has been associated with a recessively inherited insensitivity to pain [3, 12].

Aberrant vascular dynamics have been postulated as a cause of primary erythromelalgia. Vasoconstriction with reactive hyperemia seems to be the dominant mechanism in some subtypes, although in others, vasodilatation appears responsible. Mørk et al. proposed a vascular "steal" mechanism, whereby increased thermoregulatory blood flow leads to shunting with decreased nutritive perfusion and tissue hypoxia [13]. Focusing on patients with erythromelalgia involving mainly the distal lower extremities, Davis et al. noted dramatic increases in skin temperature and blood flow during attacks [14]. Davis's patients paradoxically lacked a concurrent increase in transcutaneous oximetry measurements, supporting Mørk's hypothesis. Davis showed that small fiber neuropathy and vasculopathy, with intermittent increased blood flow, coexisted in their erythromelalgia patients. He proposed that erythromelalgia may be primarily a neuropathy in which neural control of vascular tone is disturbed [14]. Both Mørk and Davis conceded that erythromelalgia is heterogeneous, with the possibility of more than one mechanism causing this phenomenon. An extensive panel of primary causes has also been reported for type 3 erythromelalgia. These include hematologic disorders, malignancy, cardiovascular disease, embolic disease, autoimmune disease, infectious disease, neurologic and musculoskeletal disorders, drugs, physical injury including frostbite, and toxins and poisons [15].

The diagnosis of erythromelalgia is made clinically based on presentation and physical symptoms, as histopathological examination is nonspecific. Unfortunately, patients are often misdiagnosed or undiagnosed for years, as symptoms may be intermittent and nonspecific in nature. Erythromelalgia presenting only with facial lesions and symptoms, as in our patient, may be especially difficult to diagnose.

Differential diagnosis varies depending on the location affected. The differential diagnosis of facial erythromelalgia includes rosacea, actinic damage, connective tissue disease, menopausal flushing, flushing related to carcinoid syndrome, and medication reactions [8, 15]. For distal extremity involvement only, diagnostic considerations would include Raynaud phenomenon, complex regional pain syndrome, venous insufficiency, peripheral arterial vascular disease, and peripheral neuropathy [13].

In a review of 32 pediatric cases of erythromelalgia from the Mayo Clinic, Cook-Norris et al. report that 66% of patients had limited activity with 13% being wheelchair-bound. In 34%, school attendance

was affected and 28% had depression, anxiety, or behavior problems. There were three deaths in the group, which were related to suicide, sepsis, and bone marrow suppression secondary to cyclophosphamide treatment. Two affected first-degree relatives were also reported to have committed suicide because of erythromelalgia [5]. In another study of 168 erythromelalgia patients in the general population from the Mayo Clinic, patients were reported to have a significant increase in disabilities, including inability to walk long distances, inability to stand for long periods, and inability to drive. Some people required wheelchair use, others were bed bound, and 12% had to give up their job. Three members of this group committed suicide because of their disease and an affected relative of one patient was also reported to have committed suicide because of the disease [4]. Although studies from a tertiary referral center may select for patients with more severe disease, the physical and psychological effect of erythromelalgia on many patients is severe.

Symptoms of erythromelalgia are often difficult to alleviate and no specific therapy has been shown to be effective in all patients. In secondary erythromelalgia, treatment of the underlying etiology is essential. Symptomatic treatment includes cooling of the limb during attacks and frequent limb elevation [15]. Topical treatments include capsaicin [16, 17], amitriptyline/ketamine [18], and lidocaine [19]. Oral treatments include selective serotonin reuptake inhibitors [20], tricyclic antidepressants [21], anticonvulsants [22], calcium channel blockers [23], and misoprostol [15]. Intravenous treatments include nitroprusside [24, 25], prostaglandin E1 [23, 26] and lidocaine [27]. Sympathetic and epidural blocks and sympathectomies are more invasive options typically reserved for more severe, recalcitrant cases [28-33]. Aspirin and hydroxyurea [3, 15] may be helpful in type 1 erythromelalgia. Mexiletine or flecainide (sodium channel blocking agents) can potentially treat the primary inherited form (type2) [34, 35]. Prognosis is variable, with 30% reported to improve, 30% to worsen, 30% to continue unchanged, and 10% to undergo complete remission [4].

In summary, erythromelalgia is a rare condition associated with burning pain, erythema, and increased temperature of the involved area. It is aggravated by heat and improved by cooling. Erythromelalgia involving only the face presents a particularly difficult diagnostic challenge. Erythromelalgia is often associated with a severe physical and psychological burden. Management of erythromelalgia is often difficult and frustrating for the patient and physician, as no single treatment is consistently effective.

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