

# A refractory case of Erythromelalgia involving the ears.

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Claudia C. Ramirez, MD, and Robert S. Kirsner, MD,

From Veterans Administration Medical Center, Miami, FL; and the Departments of Dermatology and Cutaneous Surgery; and Epidemiology and Public Health, University of Miami School of Medicine, Miami, FL.

Address correspondence to: Robert S. Kirsner, MD, University of Miami/veterans Administration Medical Center, Department of Dermatology, 1201 NW 16th Street, B1206, Miami, FL 33125. E-mail: [RKirsner@med.miami.edu](mailto:RKirsner@med.miami.edu)

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Erythromelalgia is a rare syndrome that is characterized by episodic attacks of burning pain, erythema, and increased temperature usually affecting the extremities, which is aggravated by warmth or exercise. We describe a patient with a 3-year history of refractory burning pain and red ears. A review of clinical features, disease classification, associated diseases, and treatment of this disease is presented.

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Erythromelalgia is a rare disease characterized by intense burning pain (typically of the extremities), redness, and increased skin temperature. Warmth aggravates the symptoms, whereas cold provides relief(1,2). Ice-water immersion is so common among patients with erythromelalgia that it is considered almost pathognomonic(3). Initially, 2 types of erythromelalgia were described: a primary type and a secondary type, which may occur associated with many conditions such as myeloproliferative disease, systemic lupus erythematosus (SLE), hypertension, diabetes mellitus (DM), and vasculitis(4,6). Recently, a third type has been described as a separated entity that is associated with thrombocythemia(7). Most patients experience the symptoms in the feet, but the hands may also be a primary site. Although erythromelalgia typically has a bilateral presentation, it may be unilateral, especially in secondary cases(3). In severe cases,

erythromelalgia may extend up the legs or arms, from lower to upper limbs, or to the face or ears(3). We report a rare case of refractory erythromelalgia involving only the ears.

## **CASE REPORT**

A 53-year-old Hispanic man, with a 3-year history of burning pain and redness of his ears, was referred for further evaluation and treatment. Initially, the symptoms were sporadic, several episodes monthly, related to warmth and exercise, and had gradually worsened. Several months prior, the symptoms became constant and disturbed his sleep as well. He had been treated with aspirin, various antihistamines, venlafaxine, gabapentin, diazepam, and tetracycline without relief. He was using cold water as a spray on his ears and preferred to remain in cold environments. His past medical and family history were unremarkable. Apart from the therapy for his ears, he was taking no medications.

On examination, he was healthy appearing with unremarkably general examination. On both ears, involving the entire helix and antihelix, he had pink to red, tender, and swollen plaques. He had no scale and had no involvement of his feet, hands, or other parts of his face. A biopsy of involved skin showed superficial and deep perivascular inflammation with prominent endothelial cells. Fungus and mycobacterium cultures were negative. Laboratory analysis including a complete blood count, platelet count (241,000/mL), chemistry profile, liver function tests, antinuclear antibody, and antineutrophil cytoplasmic antibodies levels were either within normal limits or negative. Serum qualitative cryoglobulin was positive (cryocrit = <0.1%, trace levels). As a result of the positive cryoglobulin, a work up to exclude viral hepatitis, multiple myeloma, Waldenstrom's macroglobulinemia, lymphoproliferative disorders, rheumatoid arthritis, and SLE was performed with negative results.

A diagnosis of primary erythromelalgia was made. He was treated with amitriptyline (35 mg/d orally), propranolol (20 mg orally twice a day), prednisone (40 mg orally every day), stanozolol (4 mg orally twice a day), nifedipine SR (30 mg orally every day), diazepam (10 mg orally twice a day), as well as superpotent topical steroids (clobetasol 0.05% cream) and topical anesthetics (lidocaine 2.5 % /prilocaine 2.5%). No significant change was noted.

## **DISCUSSION**

Classically, erythromelalgia is characterized by swollen, erythematous, and painful extremities. Intense burning pain is relieved by cooling and worsened by warming. The diagnosis of erythromelalgia is based on 5 clinical criteria proposed by Thompson et al(1): burning (extremity) pain, pain aggravated by warming, pain relieved by cooling, erythema of affected skin, and increased temperature of affected skin. Our patient had a burning distress of his ears with associated swelling, increased temperature, and redness that had been intolerable. His symptoms were relieved by cooling, by spraying cold water in both ears during most of the day. The location of the disease in our patient is atypical. In a retrospective study conducted by Davis et al(5), location of erythromelalgia in 168 patients was described. Feet were involved in 88.1%, hands in 25.6%, and legs in 13.7%.

Ears were involved in 1 patient (0.59%). Kalgaard et al(2) reported a study involving 87 patients with erythromelalgia; no patients with ear involvement were described. Histopathological findings from the skin sample showed superficial and deep perivascular inflammation with lymphocytic infiltration and prominent endothelial cells. Based on small numbers of histologic sections reported in small cases series or case reports(8), thickening of the basal membrane of capillaries, moderate endothelial swelling, perivascular edema, and a mild perivascular mononuclear infiltrate is seen in primary erythromelalgia histology(9). In addition, mild dilatation of capillaries in the superficial dermis may be present. Our patient's histological findings were consistent with the findings reported for erythromelalgia.

Secondary erythromelalgia is caused by several disorders including myeloproliferative diseases, polycythemia vera, myelofibrosis, agnogenic myeloid metaplasia, and chronic myeloid leukemia(10). Secondary erythromelalgia has also been associated with venous insufficiency, rheumatoid arthritis, hypertension, DM, gout, vasculitis, pernicious anemia, SLE, and medications (calcium channel blockers, bromocriptine, pergolide)(11,12). Secondary erythromelalgia is rare in childhood and generally affects patients over middle age, with a median age of diagnosis older than primary erythromelalgia. Unilateral or upper extremities presentation occurs mostly in secondary erythromelalgia. In the study conducted by Kalgaard et al of 87 patients with erythromelalgia, 42% had secondary erythromelalgia and the most common associated conditions were DM type 1, DM type 2, polycythemia vera, and SLE. Our patient had bilateral symptoms and an adult onset age; however, his past medical history, physical examination, or laboratory findings did not suggest an associated factor. Myeloproliferative disorders often occur a median of 2.5 years after the erythromelalgia, suggesting continued evaluation over time be periodically performed, even with a negative initial evaluation(10).

Among the differential diagnosis, relapsing polychondritis could be considered because of the location of the symptoms. This disease is characterized by intermittent episodes of inflammation of the cartilage of the ears and nose, with red and swollen ears, but sparing the ear lobes. Chondrodermatitis nodularis chronica helices is also characterized by a tender, chronic inflammatory lesion occurring on the outer helix of the ear, most frequently in man, but it also presents with nodules, which were not seen in our patient. Other considerations in the differential diagnosis include sarcoidosis, Hansen's disease, atopic eczema, fasciitis, neuropathies, vasculitis, and other vascular diseases. As shown by our patient, the treatment of erythromelalgia is often difficult(4,5). This may be because of the lack of understanding of the pathophysiology, and the prevalence of erythromelalgia needed to perform therapeutic trials. Early studies suggested that aspirin effectively relieved erythromelalgia symptoms, but aspirin appears to be significantly more effective when there is an associated thrombocythemia and polycythemia vera(3). In a retrospective study of 168 patients with erythromelalgia, 52% reported that aspirin provided no relief of symptoms on the initial presentation. Rudikoff and Jaffe(13) reported 3 remissions using venlafaxine and sertraline (serotonin reuptake inhibitors). Improvement has also been reported with fluoxetine, paroxetine, and tramadol(7). Other antidepressants such as amitriptyline and imipramine have been used with little

improvement of erythromelalgia symptoms. Nifedipine is recommended for some patients to attenuate the vasoconstriction phase of erythromelalgia, reducing the reactive hyperemia(14). Curiously, calcium antagonists have been reported to induce erythromelalgia. Other treatments include gabapentin, prednisone, benoxybenzamine hydrochloride, propranolol, intravenous sodium nitroprusside, prostaglandins, methysergide, and cyproheptadine (both antiserotonin drugs). Among topical treatment options, topical capsaicin was reported to be useful in a patient with erythromelalgia(15). Invasive approaches have been tried such as continuous epidural infusion of bupivacaine and fentanyl, sympathectomy for refractory cases, and lumbar sympathetic ganglion block.

Aspirin, calcium channels blockers, betablockers, systemic steroids, tricyclic antidepressants, gabapentin, stanozolol, benzodiazepines, superpotent topical steroids, and topical anesthetics showed little effect in our patient. This in combination with the various treatments described in the literature for erythromelalgia, often with poor results, suggest that a standard treatment for primary erythromelalgia has not been established.

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