Erythromelalgia Misdiagnosed as Cellulitis

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GOAL

To understand erythromelalgia

OBJECTIVES

Upon completion of this activity, dermatologists and general practitioners should be able to:

1. Describe the clinical presentation of erythromelalgia in patients.
2. Explain the pathophysiology of erythromelalgia.
3. Discuss the treatment options for erythromelalgia.

CME Test on page 32.

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Drs. Eaton and Murphy report no conflict of interest. The authors report off-label use of aspirin, gabapentin, heparin, lidocaine patches, misoprostol, serotonin reuptake inhibitors, ticlopidine, topical capsaicin, tricyclic antidepressants, and warfarin for the treatment of erythromelalgia. Dr. Fisher reports no conflict of interest.

This case report examines the presentation of a patient with erythromelalgia that was misdiagnosed as cellulitis on several prior occasions. The presentation of bilateral acral edema and erythema, especially in the setting of myeloproliferative and/or connective tissue diseases, should alert the physician to the possibility of alternate diagnoses, including erythromelalgia. Treatments target symptom alleviation, as well as diagnosis and treatment of causative factors.

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Erythromelalgia is a rare syndrome that is characterized by intense burning pain, erythema, and warmth of the acral sites. The feet are predominantly involved with the hands being the second most common site.[1] A primary form exists that usually presents in adolescence or youth; secondary forms usually present later in life and are attributed to various causes such as myeloproliferative diseases, connective tissue disorders, diabetes mellitus, and medication use, among others.[2] Diagnosis is based on the patient's medical history and clinical findings.

Treatment strategies include removal of the offending agents or processes, symptomatic relief with cooling agents and/or pain medications, and medications that target the pathophysiology involved, namely microvascular injury and thrombosis.[1]

Case Report

A 55-year-old white woman reported to the dermatology department for evaluation of onychomycosis. She was an inpatient at a tertiary hospital who was receiving intravenous antibiotics for a diagnosis of chronic recurrent cellulitis; it was thought that her chronic onychomycosis was the portal of entry for these recurrent infections. The symptoms of this episode began 2 days prior, when she noted bilateral swelling of the feet and lower legs and burning accompanied throughout the day by increased redness and pain, similar to her 7 previous episodes over the past 1½ years. She stated that she experienced chills but no other constitutional symptoms of fever or rigor. It was noted that her feet and legs did feel warm.

The patient's medical history included polycythemia vera diagnosed several years prior that was treated with phlebotomy and aspirin 325 mg daily; diabetes mellitus, for which she was taking metformin; hypertension, for which she was treated with nifedipine and valsartan; and recurrent cellulitis, for which she had been taking prophylactic clindamycin since her previous admission 1.5 months prior.

Results of a physical examination revealed an afebrile woman with nontender distal edema of the bilateral lower extremities. Erythematous dorsal feet, ankles, and distal lower extremities also were noted (Figure). No ulcerations were present, and no regional lymph nodes were enlarged or tender. Nails were dystrophic and thickened.

Laboratory test results revealed an elevated white blood cell count of $15.4\times10^3/\mu L$, hemoglobin level of 10.6 g/dL, hematocrit level of 34.3%, and platelet count of $405\times10^3/\mu L$.

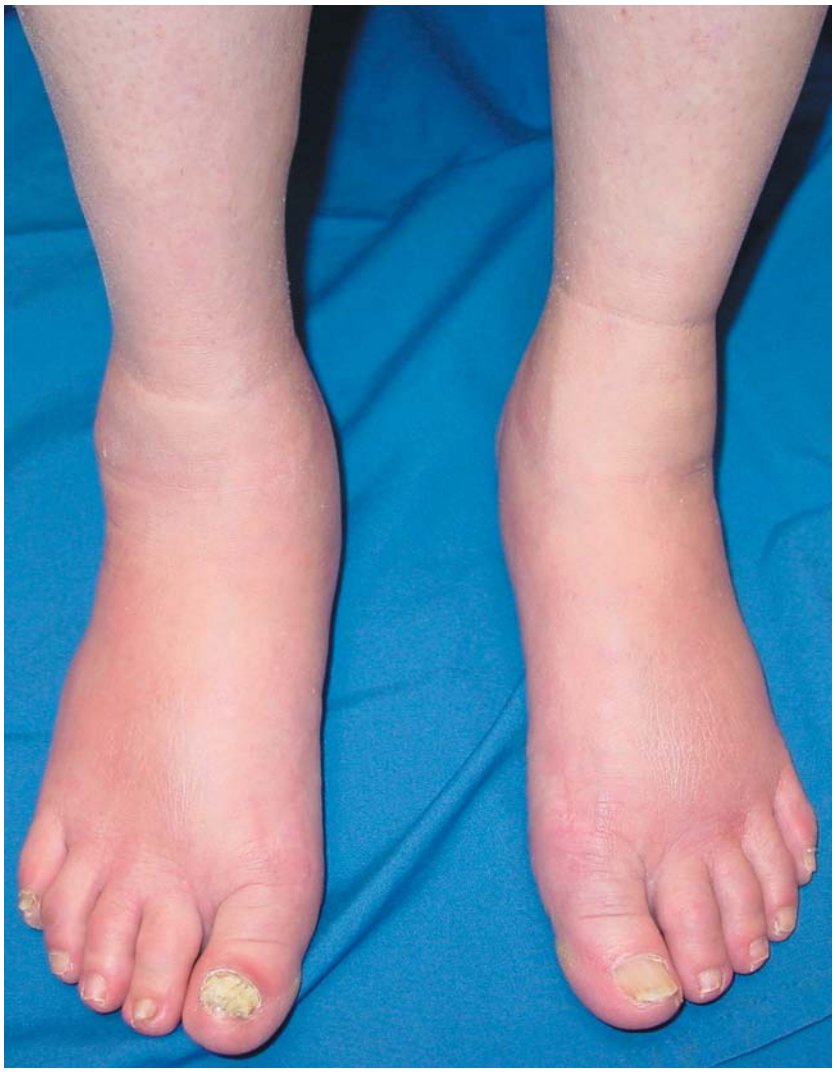
On admission, blood cultures were drawn, and the patient was given vancomycin (she was allergic to penicillin and nafcillin). During an interview the following day, it was noted that her symptoms began synchronously with her use of nifedipine 18 months prior. The symptoms had never fully resolved between the onset of the event and admission to the hospital, and the symptoms were incited by dependence of the legs and exercise. The dermatology consultant diagnosed erythromelalgia instead of cellulitis and recommended treatment with ice applications, cool water immersion baths, and discontinuation of the calcium channel blocker in favor of a β-blocker for her hypertension. The patient was advised to continue taking aspirin daily, and the treatment team was advised to search for further connective tissue disease via laboratory examination. The patient was discharged that day; at her 10-day follow-up, symptoms had totally resolved with the discontinuation of nifedipine and the initiation of propranolol. At one month postdischarge, the patient's symptoms remained absent.

Comment

Erythromelalgia is a striking pain syndrome that occurs almost twice as often in women as in men.[1] Primary disease with early onset is especially rare, with less than 30 cases reported in the literature. Secondary disease, especially that related to myeloproliferative disorders, is less rare, with an estimated incidence of 2.5 to 3.3 cases per million people per year.[3]

The pathophysiology of erythromelalgia is not completely understood but seems to involve a number of contributing factors. In erythromelalgia secondary to thrombocythemia, microthrombi and arteriolar fibrosis have been demonstrated, as well as intrinsic platelet defects such as an increased propensity to aggregate and shortened platelet survival.[4] Primary disease, which frequently does not demonstrate such platelet findings, demonstrates abnormal vascular dynamics resulting from arteriovenous shunting and a mismatch between thermoregulatory and nutritive perfusion.[5] Another postulation is dysfunctional sympathetic vasoconstrictor response.[6] Davis et al[7] have demonstrated in a prospective study that most patients with erythromelalgia, in addition to other forms of neuropathy, also have small fiber neuropathy. Determining the likely pathogenesis based on the clinical presentation is important in developing a treatment strategy.

The clinical presentation of erythromelalgia is similar to that described in this case report. Burning, erythema, and warmth of acral sites are the predominant features and may be present constantly, wax and wane, or disappear entirely between episodes.[1] These episodes can last hours, days, months, and even seasons, and are frequently associated with exacerbating factors such as heat, exercise, fever, and dependent posture.[2] If left untreated, erythromelalgia can progress towards acrocyanosis and even peripheral gangrene.[1] In the largest study to date, Davis et al[1] noted a significant decrease in survival compared with age- and gender-matched controls. This same study pointed to an overrepresentation of death by suicide, myeloproliferative disease, and connective tissue



Erythematous and edematous distal extremities seen in erythromelalgia.

disease compared with the general population. The clinician cannot overestimate the effect of this disease on the patient.

Diagnosis can be difficult because erythromelalgia is purely a clinical diagnosis and confusion exists as to the diagnostic criteria. Thompson et al[8] proposed the following 5 criteria in 1979, and most trials since then have made attempts to conform as closely as possible in defining inclusion criteria: (1) burning extremity pain, (2) pain aggravated by warming, (3) pain relieved by cooling, (4) erythema of affected skin, and (5) increased temperature of affected skin. Laboratory examination and/or biopsy specimens of the affected areas are important only in the exclusion of underlying diseases. The differential diagnosis is varied and includes reflex sympathetic dystrophy, angiodyskinesia, acrocyanosis, peripheral neuropathy, and lipodermatosclerosis.[1,2]

Treatment strategies are formulated in the context of causative factors. Diagnosis and treatment of the underlying disease process is paramount in alleviating erythromelalgia but is not always successful. In erythromelalgia secondary to thrombocythemia, especially in polycythemia vera, antiplatelet therapy is usually helpful. Aspirin is the first-line treatment of choice because its effects are longer lasting. Other nonsteroidal anti-inflammatory drugs may be substituted in the event of aspirin sensitivity.[1] Alternative antiplatelet medications such as ticlopidine, warfarin, and heparin have not been shown to be effective.[4] Removal of causative medications should be investigated and is diagnostic when successful. Implicated medications include nifedipine, pergolide, bromocriptine, felodipine, and nicardipine.[9] Symptomatic treatment with lifestyle changes is a cornerstone of treatment and involves a reduction in exposure to exacerbating factors such as heat, exercise, fever, and dependent posture, as well as the application of cooling modalities, elevation of affected areas, and rest. The addition of some medications is often beneficial, and case reports have noted numerous medications to be helpful. As of yet, no large well-designed trial has been conducted to fully elucidate which medications are most effective. In cases refractory to the above strategies, topical and oral medications used in treating neuralgias may be helpful. Some of the medications mentioned in the literature include lidocaine patches, topical capsaicin, tricyclic antidepressants, serotonin reuptake inhibitors, and gabapentin.[1,2] Prostacyclins such as misoprostol have been discussed, as well.[10] Consideration should be given for referral to a chronic pain clinic for these and other treatment modalities.

Conclusion

Erythromelalgia is a difficult diagnosis to make and often is a difficult disease for the patient to endure. Special care should be taken by the clinician to

search for an underlying disorder when this diagnosis is made and during follow-up. Treatment is directed at the underlying cause, if discernible, and at the symptomatic relief of the patient. Prognosis is mixed; approximately the same number of individuals will improve, remain stable, or worsen, even with referral to a large tertiary care setting with multiple resources.[1]

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