CLINICAL VIGNETTE

Erythromelalgia in association with Multiple Myeloma

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Introduction

Erythromelalgia is an uncommon disorder associated with both a small fiber neuropathy and vasculopathy caused by a transient blockage of blood vessels in the extremities.[1] Clinically, this causes increased temperature and redness of the skin with intense burning pain and without evidence of arterial occlusion.[2] Symptoms usually manifest after exposure to heat and are alleviated by cooling the skin, elevating the affected extremity or treating with aspirin.[2]

The disorder can be separated into two distinct forms. Primary erythromelalgia is an autosomal dominant disorder caused by a mutation in the *SC9A* gene that codes for voltage-gated sodium channels alpha subunit.[3] Secondary erythromelalgia occurs in association with a secondary disease process, most commonly myeloproliferative syndromes.[4] Even though an association between myeloproliferative disorders and erythromelalgia is well documented, a specific association with multiple myeloma has yet to be reported. We propose that erythromelalgia should be considered to be a complication of multiple myeloma as well.

Report of Case

A 68-year-old male presented with painful burning and erythema of the feet bilaterally after using a heating pad. The patient had been diagnosed with IgG κ multiple myeloma. Several therapies were initiated including Lenalidamide (*Revlimid*) and Bortezomib (*Velcade*) in the months prior to presentation. This treatment was subsequently terminated secondary to development of histiocytoid Sweets syndrome. Shortly after termination of this medication and two weeks prior to presentation, the patient developed erythema and an "eight out of ten" burning pain of his bilateral plantar feet that disturbed his sleep. This was precipitated by heating pad use. Symptoms were alleviated only with ice. He sought evaluation at an urgent care center where he was given topical bacitracin, neomycin, polymyxin B, and clotrimazole ointment for a suspected diagnosis of a first-degree burn and tinea pedis, respectively. Both treatments did not provide any alleviation. Review of systems revealed an 18-pound weight loss and decreased appetite over the preceding two months.

Other medical history included: schizophrenia, benign prostatic hyperplasia, inflammatory bowel disease, hypothyroidism, and Parkinson's disease. He had no history of peripheral neuropathy. Past surgical history and family history were unremarkable. Allergies include velcade and sulfa antibiotics. Medications include alprazolam, lenalidomide, levothyroxine, propranolol, risperidone, and temazepam.

On initial evaluation at our institution, the patient was alert, oriented, and appeared to be in no acute distress. Bilateral plantar feet were diffusely erythematous, warm, tender to palpation, and with mild scale (Figure 1). Review of systems was otherwise negative. The remainder of his exam, including the hands, was normal.

Upon diagnosis of IgG κ multiple myeloma, the patient's lab work had revealed an elevated IgG κ monoclonal gammopathy (3520 mg/mL) with an IgA of 84 mg/mL and an IgG of 16 mg/mL. The monoclonal peak noted by SPEP measured 3100 mg/mL and immunofixation of the urine revealed free κ light chains and trace amounts of IgG κ. At the time of presentation, laboratory evaluation included a complete blood count with differential, comprehensive metabolic panel, LD, total protein, β2 microglobulin.and κ, λ light chain ratio, all of which were normal. Nerve conduction studies were performed and found to be consistent with a small-fiber neuropathy.

Due to the abnormal nerve conduction studies, treatment for neuropathy was attempted with gabapentin. This failed to alleviate his symptoms and treatment was abandoned. The characteristic presentation of burning pain and redness of the distal extremities instigated by the application of a heating pad and the presence of an underlying hematologic malignancy, combined with the failure of treatment for an underlying peripheral neuropathy, led to a diagnosis of erythromelalgia. We suspect the recent discontinuation of treatment for the Multiple Myeloma two weeks prior to onset of symptoms may have contributed to the development of the erythromelagia in this patient.

Comments

The clinical triad of erythema, increased temperature, and intermittent pain in the extremities defines both primary and secondary erythromelalgia. The diagnosis is made clinically. Erythromelalgia is more common in the lower extremities and peripheral pulses are usually normal.[5] The incidence of erythromelalgia increases with age.[4,5] Increasing the skin temperature above 32 degrees centigrade can reproduce symptoms, and as such, most cases are reported in the summer months. Aspirin provides relief of symptoms. These two

clinical characteristics are described in the literature to be utilized as diagnostic tests.[6] The clinical triad, involvement of lower extremities with normal peripheral pulses, onset with application of heat, particularly in a summer month, and elderly age are all consistent with this patient's presentation.

Histopathologic findings are non-specific, but a decrease in small nerve fiber density is noted in some cases.[7] A study by *Davis et al*[8] describes that small-fiber neuropathy is common in many patients with erythromelalgia with 88% showing abnormal thermoregulatory sweat test results (n=32). In another study by *Davis et al*,[1] 58% of patients with erythromelalgia had abnormal electromyographic results and 42% had an abnormal nerve conduction study result. Blood work is usually normal; however, an elevated platelet count has been seen in patients with thrombocythemia-related erythromelalgia, and other abnormal blood counts may also indicate an underlying myoproliferative disease.[2]

Secondary erythromelalgia has been observed in patients with numerous concomitant medical conditions including myeloproliferative disease, hypertension, venous insufficiency, diabetes mellitus, systemic lupus erythematosus, rheumatoid arthritis, lichen sclerosis, gout, spinal cord disease, and multiple sclerosis.[2] Of these, the most common association is that of eyrthromelalgia and underlying myeloproliferative disease. *Babb et al*[4] reported that 41% of 51 patients presenting with erythromelalgia concurrently presented with a myeloproliferative disorder. Reported myeloproliferative disorders associated with erythromelagia have included essential thrombocythemia, polycythemia vera, agnogenic myeloid metaplasia, and chronic myelogenous leukemia (CML).[2] Most reported cases describe development of erythromelalgia prior to the onset of the underlying myeloproliferative disorder. However, in cases where a myeloproliferative disorder preceded the onset of erythromelalgia, the time between the two disorders was almost a decade[9]—consistent with the reported case above. Despite the known association between erythromelagia and myeloproliferative disorders, there have not been reports of erythromelagia with underlying multiple myeloma specifically.

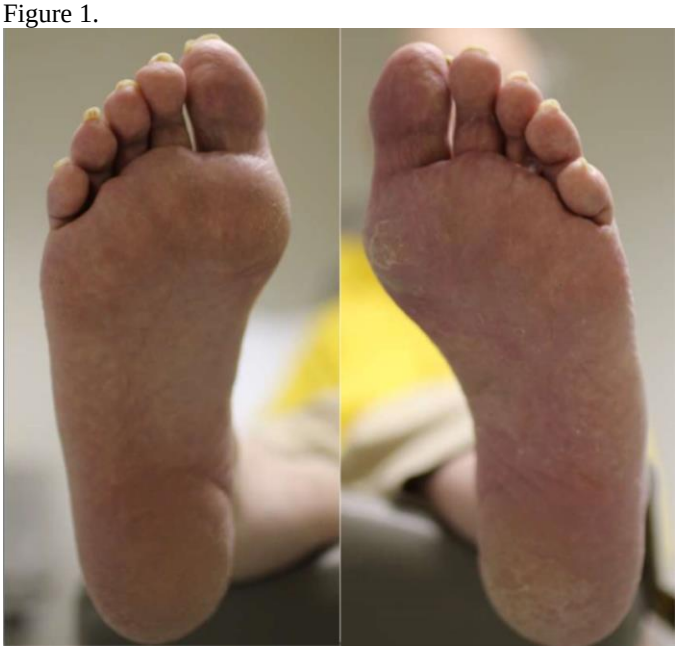
The pathogenesis of erythromelalgia is elusive with features of both a vasculopathy and neuropathy. Platelet kinetic studies show that during flairs there is activation and aggregation of "hypersensitive" thrombocythemic platelets, leading to occlusion of the microvasculature.[10] A study by *Mork et al*[11] used laser doppler-perfusion imaging and confirmed the formation of arteriovenous shunts in the region during erythromelalgia episodes. Most patients with erythromelalgia also have postganglionic pseudomotor failure localized to the periphery without evidence of more generalized autonomic failure.[1] These observations support that a small nerve neuropathy, sparing larger nerve fibers, may also contribute to the pathogenesis of erythromelalgia. It remains possible that erythromelalgia may be a heterogeneous disorder with more than one mechanism contributing to its pathogenesis.

Treatment of erythromelalgia is challenging. Reported treatments have included aspirin, nonsteroidal anti-inflammatory drugs, opioids, β-blockers, antihistamines, vasodilators, anticonvulsants, antidepressants, clonidine, corticosteroids (oral and topical), lidocaine (topical), mexiletine, and misoprostol. In 2013, *Poterucha et al*[12] reported that topical application of a compounded amitriptyline-ketamine formulation was effective in 75% of patients with secondary erythromelalgia (n=32) with minimal adverse side effects. A retrospective study by *Davis et al*[13] sought to evaluate the efficacy of current erythromelalgia treatment and none of the drugs examined were found to be universally helpful to relieve the symptoms (n=168). Because of lack of consensus for therapy, a trial and error method is usually undertaken until adequate therapy is achieved.

In summary, the association between erythromelalgia and myeloproliferative disorders is accepted, but recognition of erythromelagia in the context of multiple myeloma has not been reported. This case illustrates an example of erythromelalgia of the bilateral feet in a patient with underlying multiple myeloma. It is important the dermatology community recognizes this association to effectively diagnose and treat patients with these comorbidities.

Figures

Figure 1.



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