

BRIEF ARTICLES

Erythromelalgia in a Patient with Mast Cell Activation Syndrome: Response to Low Dose Naltrexone

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ABSTRACT

Erythromelalgia is a rare condition that may be associated with a variety of underlying conditions and is often refractory to therapy. We report a case of a patient with mast cell activation syndrome who developed erythromelalgia and responded to low dose naltrexone.

INTRODUCTION

Erythromelalgia (EM) can be disabling and difficult to treat. The incidence is 1.3 per 100,000 people per year.¹ Diagnostic criteria include: burning pain and erythema of the extremities, pain aggravated by warming/relieved by cooling, and increased skin temperature.² Affected areas usually appear red and edematous and can have associated acrocyanosis, livedo reticularis, facial flushing, cutaneous necrosis and ulceration. The three major forms include: Type 1 – associated with thrombocythemia; Type 2 – primary, familial, or idiopathic; and Type 3 – associated with vascular and autoimmune diseases. Familial EM has been linked to dominant gain-of-function missense mutations in the SCN9A gene, which encodes the voltage-gated sodium channel alpha subunit Na(v)1.7, thought to be involved in nociception.³

There is no definitive treatment for EM. We present a case of a patient with mast cell

activation syndrome (MCAS) and EM, who had a good response to low dose naltrexone (LDN).

CASE REPORT

A 55-year-old Caucasian female presented with an 8-month history of EM prior to our evaluation. The patient reported bilateral feet symptoms of burning pain, pricking sensation, and temperature changes ranging from hot to cold. She could not wear shoes without severe pain. Treatment with aspirin, nortriptyline, diltiazem, and topical nifedipine failed to provide relief. Gabapentin marginally reduced her pain. Metoprolol worsened the pain. She had a history of Raynaud's phenomenon since age 15. Review of systems revealed a long history of fatigue, eye irritation, mouth sores, chest pain, palpitations, near syncope, bloating, abdominal pain, alternating diarrhea and constipation, heartburn, frequent urination, chronic headaches, muscle pain, anxiety, depression, brain fog, alopecia, and easy bruising.

Physical examination was remarkable for symmetrical erythema and edema of bilateral lower extremities without evidence of temperature difference between the feet and legs (Figure 1).

Figure 1. Erythema and edema of right foot.



Skin punch biopsies of the calf and thigh were performed by her prior clinician to evaluate for small fiber neuropathy in the work up of dysautonomia, and were negative. Complete blood count was within normal limits. Mast cell mediators (plasma prostaglandin D2, histamine, and heparin; serum tryptase and chromogranin A; and 24-hour urine N-methylhistamine, leukotriene E4, and prostaglandin 11- β -PGF2 α) were obtained when she was feeling generally well and were normal. Duodenal biopsies revealed 30-40 mast cells per high power field. She fulfilled the criteria for MCAS by having characteristic symptoms in 2 or more

systems and having a mast cell density ≥ 20 per high power field.⁴

Mast cell-directed therapy was initiated with trials of various histamine 1 and 2 receptor blockers, including ranitidine, famotidine, ketotifen, and loratadine. These medications initially helped reduce her allergic, cardiac, and gastrointestinal symptoms. After 1 month, LDN was added at 1 mg daily and gradually increased to 3 mg daily over 2 months. Naltrexone was compounded into capsules by a compounding pharmacy. The histamine blockers were discontinued due to worsening constipation.

After two months of LDN therapy, she reported moderate improvement in EM symptoms with reduced pain flares in her feet. At a clinic visit, eleven months after initiating LDN, she reported reduced pain, erythema, and edema in her feet (Figure 2). She estimated a subjective clinical benefit of 75% that has been maintained with 2 years of LDN therapy. She is able to wear shoes comfortably most of the time, but reported self-limited erythema after exercise walks. She was unable to increase the LDN dose to 4.5 mg due to insomnia but was able to tolerate 3 mg each morning. LDN was continued at 3 mg for 2 years with continued symptom improvement in the extremities (Figure 3). LDN also helped reduce bruising, chest pain, and mouth sores.

DISCUSSION

In this case, LDN helped reduce the severity of EM in a patient with concomitant MCAS.

MCAS is a chronic multi-system disease of abnormal mast cell activation that leads to inflammatory and allergic illness. MCAS has been estimated to have a prevalence of up to 17% (in the German general population);

SKIN

Figure 2. Improvement after 11 months of LDN therapy.



Figure 3. Continued improvement after 2 years of LDN therapy.



however, the actual prevalence is not known, as MCAS is often not considered in the differential diagnosis of complex patients.^{4,5} Unrecognized and untreated, MCAS may account for many refractory and vexing dermatologic symptoms. These include urticaria, pruritis, flushing, hemangiomas, and angioedema. The symptoms of MCAS can be numerous and affect multiple organs and systems which further complicates the clinical presentation.

LDN has been successfully used off-label as an anti-inflammatory and immunomodulatory agent in several dermatologic conditions.⁶⁻⁸ The LDN dose typically ranges from 1.0 to 4.5 mg daily. The duration of the opioid receptor blockade determines naltrexone's biotherapeutic response.⁹ Sustained inhibition of mu-opioid receptors by high dose naltrexone has been shown to increase inflammation and proliferation of tumor cells, while intermittent blockade by LDN inhibits cellular proliferation of T and B cells and antagonizes the Toll-like receptor 4 (TLR4)-mediated pro-inflammatory pathway in macrophages and microglia. Increasing evidence suggests that the immune system, specifically the TLR4 pathway, plays an integral role in maintenance of chronic pain.¹⁰ Mast cells are known to express TLR4 receptors and participate in nociception.¹¹

Although the pathophysiology of EM is multifactorial and poorly understood, there may be altered inflammatory mediator expression which results from vascular and/or neuronal dysfunction and which may benefit from immune modulators. A search for an underlying cause of presumed idiopathic EM should be thoroughly pursued. Further studies are necessary to evaluate the therapeutic benefit of LDN in patients with EM.

Conflict of Interest Disclosures: None

Funding: None

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