

A Case of Erythromelalgia: Good Response to Combination Treatment with Pregabalin and Selective Serotonin Reuptake Inhibitor

Atiye Oğrum,¹ MD, Zennure Takçı,^{2*} MD, Güler Vahaboğlu,³ MD, Hatice Meral Ekşioğlu,³ MD

Address: ¹Department of Dermatology, Tokat State Hospital, Tokat, ²Department of Dermatology, Gaziosmanpasa University, Faculty of Medicine, Tokat, ³Department of Dermatology, Ankara Research and Training Hospital, Ankara, Turkey

E-mail: drzennure80@yahoo.com

* Corresponding Author: Dr. Zennure Takci, Department of Dermatology, Gaziosmanpasa University, Faculty of Medicine, Tokat, Turkey

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Abstract

Observation: Erythromelalgia is a rare entity characterized by episodic acral burning pain, heat and redness in the extremities. Symptoms are triggered by a warm environment and can be relieved by cooling. The pain may be severe enough to disrupt a person's quality of life. The cases in which there is no underlying disease are known as primary, whereas the cases associated with different diseases are known as secondary erythromelalgia. Here, a case of erythromelalgia, secondary to type 2 diabetes mellitus, is presented, with a good response to treatment with a combination of selective serotonin reuptake inhibitors and pregabalin.

Introduction

Erythromelalgia is a rare condition that is occasionally characterized by severe burning pain and redness in the extremities, especially in the feet. Symptoms are triggered by physical exertion or a warm environment, and can be relieved by cooling or the elevation of the limbs. This condition can be primary or secondary to systemic disease [1, 2, 3, 4, 5, 6]. Secondary erythromelalgia usually resolves with treatment of the underlying disease. A wide variety of treatments, such as acetyl salicylic acid, gabapentin [7, 8], serotonin and noradrenaline reuptake inhibitors [9], serotonin reuptake inhibitors [10, 11], calcium channel blockers, prostaglandin E1, nitroglycerin, sympathetic blockage [12], sympathectomy, etc., have been tried. Here, a case of erythromelalgia, secondary to type 2 diabetes mellitus, is presented, with a very good response to treatment with the combination

of selective serotonin reuptake inhibitors and pregabalin.

Case Reports

A forty-five year-old Caucasian woman was admitted to the dermatology clinic with complaints of burning pain, oedema, warmth, redness and shallow wounds on both legs, which began about 2 years previously. These symptoms increased during the summer and decreased with cold application and in the winter. She had received various antibiotic treatments for the infections; but the complaints had not decreased.

This patient had been receiving insulin therapy, with a diagnosis of type 2 diabetes mellitus, for 10 years. She denied similar symptoms among family members, and there was no family history of erythromelalgia. The physical examination was normal; however, upon dermatological examination, there was oedema and diffuse erythema decreasing with pressure on both distal lower extremities (Figure 1), and 5 separate 1 cm diameter superficial ulcers



Figure 1. Erythema and edema in the lower extremities (before treatment)

on her ankles. The complete blood count, metabolic panel (except for fasting and postprandial blood glucose values), sedimentation rate, thyroid function tests, protein electrophoresis, hepatitis B and C serology, anti-HIV, RF, ANA, anti-ds DNA, C3, C4, Ig G, Ig M and Ig A levels were within normal limits or negative. Her fasting blood glucose was 225 mg/dl and her postprandial blood glucose was 310 mg/dl. The chest x-ray and arterial and venous Doppler ultrasonography of both lower extremities were normal. This patient was consulted to the Department of Neurology, and bilateral diffuse peripheral sensorimotor polyneuropathy was seen upon electromyography. This polyneuropathy was evaluated as secondary to diabetes mellitus.

The patient was diagnosed as having erythromelalgia, using the clinical and laboratory findings. The regulation of her blood glucose was achieved by working with the Department of Endocrinology. Gabapentin (800 mg/d) was initiated and raised to 2400 mg/d at 4 months, but due to the insufficient response and drug-related headaches, the gabapentin was stopped. She was then started on 150 mg/d pregabalin, and this was increased to 300 mg/d after 1 week. Minimal improvement was obtained at 2 months, then Sertraline HCl (serotonin reuptake inhibitor) at 50 mg/d was added to the pregabalin treatment. Good clinical improvement was obtained with this combination therapy after 1 month (**Figure 2**). The patient's treatment and follow-up continued for sixteen months.



Figure 2. Decreasing of erythema and edema and in the lower extremite (after treatment)

Discussion

Erythromelalgia was first described by *Mitchell* in 1878, is usually episodic, and rarely continuous. It is described as acral burning pain, redness, oedema and warmth of the feet and/or hands, which increases with heat and decreases with cold [4]. The pathophysiology is not well understood, but it is thought to be due to an increased blood flow in the microvascular shunts, and tissue hypoxia in the skin [4] This may be primary or secondary to various conditions, including haematological diseases, cardiovascular system diseases, autoimmune diseases and drugs [1,2,3,5].

Primary erythromelalgia can be very resistant to treatment, and improvement in the secondary form is usually obtained with the treatment of the underlying disease. A standard treatment protocol is not available; however, treatment methods include non-steroidal anti-inflammatory drugs such as acetyl salicylic acid, indomethacin, beta blockers, antidepressants, anticonvulsant agents (gabapentin, carbamazepine, etc.), prostaglandin E1, topical nitroglycerin, capsaicin, dipyridamole, mexiletine hydrochloride, sympathetic blockade and sympathectomy [7,8,9,12].

This patient was diagnosed with erythromelalgia using the clinical and laboratory findings. Because of the presence of a ten-year history of type 2 diabetes mellitus, and bilateral common peripheral sensorimotor polyneuropathy, the patient was evaluated as having secondary erythromelalgia.

After the diagnosis of erythromelalgia secondary to diabetes mellitus, treatment was started with blood glucose regulation. No clinical improvement was seen after the blood glucose regulation, so the addition of other agents for the treatment was commenced. Gabapentin is an δ -aminobutyric acid (GABA) analogue of the anticonvulsant agents, and good responses for erythromelalgia and neuropathic pain with gabapentin have been reported [7, 8]. It shows its effects by binding to the voltage-dependent calcium channels' $\alpha 2\delta$ subunit.

Gabapentin treatment was stopped in this patient because of drug-induced headaches, and no clinic improvement after 4 months. Pregabalin, which is a structural analogue of GABA, was started at 150 mg/d, and increased to 300 mg/d, with minimal clinical improvement obtained after 2 months. A good response to selective serotonin reuptake inhibitors has been reported in the literature [9]. This suggests that the disease can occur as a result of peripheral serotonin activity. Sertraline (50 mg/d) was added to the treatment. Significant improvement was obtained with the combination after 1 month, and the patient's treatment and follow-up continues (Figure 2).

Erythromelalgia significantly affects a patient's quality of life; however, it is a difficult disease to treat. There are very few reports in the literature of gabapentin or serotonin reuptake inhibitors successfully treating erythromelalgia, and no reports about treatment with pregaba-

lin and serotonin reuptake inhibitors. This combination can be a new alternative treatment option for erythromelalgia.

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