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CASE REPORT

Verapamil-induced erythermalgia

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ABSTRACT

Erythermalgia is a rare clinical syndrome characterised by intermittent, usually symmetrical burning pain, warmth and dermal erythema of the extremities with an amelioration of discomfort by cooling of the extremity. In this report, we describe a patient with erythermalgia caused by long-term verapamil use. After discontinuing the verapamil, the symptoms improved dramatically within two weeks.

KEYWORDS

Calcium antagonists, erythermalgia, erythromelalgia, verapamil

INTRODUCTION

Erythromelalgia and erythermalgia are rare disorders characterised by severe burning pain, warmth and redness of the extremities. Symptoms are commonly exacerbated by exposure to heat and improved by cooling of the extremity. The term erythromelalgia derived from the Greek words erythros (red), melos (extremity) and algos (pain) was introduced by Mitchell.[1] Smith and Allen have suggested changing the name to erythermalgia in order to emphasise the importance of the increased skin temperature (thermé).[2] Since then, these terms are used indiscriminately as synonyms, which may cause confusion. At present two competing classifications exist. In the classification by Kurzrock *et al.* patients are categorised into early-onset erythromelalgia and adult-onset erythromelalgia (secondary or idiopathic forms).[3] Early-onset erythromelalgia manifests in childhood or during adolescence and often shows a familial occurrence. Adult-onset erythromelalgia may be associated with a myeloproliferative disorder such as thrombocythaemia, as well as with other diseases and several drugs. On the other hand, Michiels *et al.* distinguish three categories: erythromelalgia, and primary and secondary erythermalgia.[4,5] Erythromelalgia is aspirin sensitive and invariably associated with thrombocythaemia. Erythromelalgia is usually asymmetrical, whereas erythermalgia is symmetrical. Primary erythermalgia occurs spontaneously in childhood or adolescence in the absence of any detectable underlying disorder. Secondary erythermalgia originates from associated disorders or develops as a consequence of side effects of drugs. We describe a patient with secondary erythermalgia due to long-term treatment with verapamil.

CASE REPORT

In May 2002, a 66-year-old man developed recurrent attacks of redness, swelling and painful burning sensations of both feet, occurring particularly in a warm environment and during evenings. Attacks lasted several hours and the unbearable burning pain was relieved only by immersion of his feet in ice cold water. Symptoms were particularly provoked by exertion, eventually limiting his walking distance to 10 m. As a result, he was practically housebound. He reported no fever, arthralgia or increased bleeding tendency. His history included chronic atrial fibrillation. Physical examination showed red, warm, oedematous feet with intact peripheral arterial pulsations (*figure 1*). His pulse was irregular with a frequency of 70 beats/min. During a period of 14 months, he was evaluated by many specialists, including vascular surgeons, rheumatologists, internists, neurologists and pain specialists. Extensive laboratory tests showed no abnormalities. Ankle-brachial pressure index and angiography of the legs were normal. Electromyography showed no signs of polyneuropathy. Numerous pain killers such as high-dose aspirin, nonsteroidal anti-inflammatory drugs, COX-2 antagonists and morphinomimetics, as well as acenocoumarol and clopidrogel, were tried without any improvement in his symptoms (*figure 2*). Transdermal

Figure 1. *Bilateral erythromelalgia with red, warm oedematous feet*

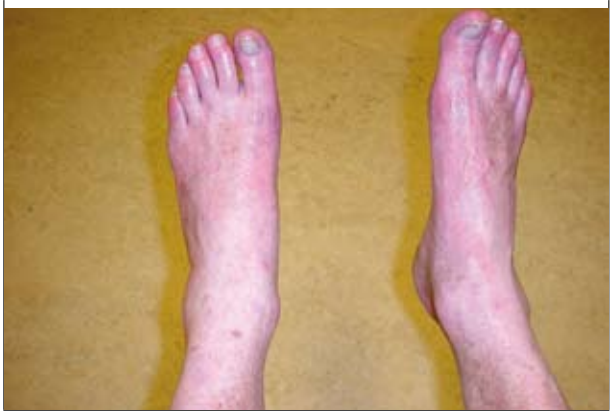

Figure 2. *Bag full of pills with which the patient presented*

electric nerve stimulations (TENS) and various homeopathic drugs were not helpful either. Chemical symphathectomy, performed three and 12 months after his first presentation, only aggravated his symptoms. The symptoms gradually worsened and were eventually present constantly throughout the day and night, making normal life almost impossible.

In July 2003, he was referred to our department. At this time, he was taking gabapentin, various homeopathic drugs and using a TENS device to reduce his pain. We established a diagnosis of erythermalgia. Evaluation of all the previously performed tests did not reveal an underlying cause for erythermalgia. However, our attention was drawn to the fact that he had been taking long-acting verapamil (Isoptin SR 120 mg/day) for the last six years for his chronic atrial fibrillation. After consulting his cardiologists we stopped the verapamil and started digoxin. Within two weeks, his complaints improved dramatically and at this moment, three years later, he is completely free of symptoms.

DISCUSSION

Drug-induced erythermalgia has been described in association with long-term use of ergot derivatives such as bromocriptine and pergolide.[6] Five case reports have reported erythermalgia caused by calcium antagonists (*table 1*). To the best of our knowledge, this is the second report of erythermalgia as a side effect of verapamil. The long time interval (five years) between the first dose of verapamil and the occurrence of erythermalgia, as described in this case, has not been reported before. Erythermalgia secondary to drugs develops insidiously and disappears within a few weeks after discontinuation. Our patient, understandably, declined a rechallenge, but rapid regression of symptoms immediately after withdrawal strongly suggests a causal relationship. Verapamil is a widely used drug and is indicated for the treatment of hypertension, cardiac arrhythmias and angina pectoris. It is a phenylalkylamine derivative which inhibits the slow inward current of calcium ions across the cell membrane of

Table 1. *Case reports on calcium antagonists-induced erythromelalgia*

Year	Author	Drug	Dose (mg/day)	T1	T2
1983	Brodmerkel[7]	Nifedipine	40	NS	Immediate
1983	Fisher *et al.*[8]	Nifedipine	60	8 weeks	2 days
1989	Levesque and Moore[9]	Nicardipine	60	3-4 weeks	'Rapidly'
1992	Drenth *et al.*[10]	Verapamil	120	Few months	1-2 weeks
1996	Sunahara *et al.*[11]	Nifedipine	40	1 day	24 hours
2007	Nanayakkara *et al.* Current report	Verapamil	120	5 years	2 weeks

T1 = time between first dose and onset of erythromelalgia; T2 = time from discontinuation of the calcium antagonist to resolution of erythromelalgia; NS = not specified.

smooth muscles, thereby causing coronary and peripheral vasodilatation. The mechanism of verapamil-induced erythermalgia is unknown, but presumably is related to its vasodilatory action. Interestingly, nifidepine and diltiazem have been used successfully for the treatment of erythromelalgia.[12]

The underlying mechanism of erythermalgia is not known. Recently the origin of primary erythermalgia (or early-onset erythromelalgia) has been revealed.[13] This autosomal dominant disorder is a neuropathic disorder and may be caused by a mutation in SCN9A, the gene that encodes the Nav1.7 voltage-gated sodium channel which is predominately expressed in sensory and sympathetic neurons. Although this mutation causes membrane depolarisation in both types of neurons, it causes hyperexcitability in sensory neurons and hypoexcitability in sympathetic neurons.[14]

Nevertheless, it is generally believed that erythermalgia is primarily a vascular disorder which may be caused by an increased vasodilatation of the microvasculature in the extremities.[15] In general, vascular tone is regulated by many factors such as nitric oxide and other vasoactive substances, sympathetic and parasympathetic nervous system. Disturbance of one of these factors could deregulate the vascular tone. It may be argued that vasodilatation in patients with inherited erythermalgia may be induced by neuronal deregulation in two ways. Firstly, a decreased stimulation of sympathetic neurons may cause vasodilatation. Secondly, stimulated sensory neurons can induce neurogenic dilatation which is mediated by calcitonin gene-related peptide (CGRP).[16] Therefore, hyperexcitability of sensory neurons may also increase neurogenic dilatation.

Drugs such as calcium antagonists are also known to induce vasodilatation by inhibiting Ca^{++} influx into vascular smooth muscle. This vasodilatation may have played a decisive role in the induction of symptoms of erythermalgia in our patient. Presumably, the chemical sympathectomy enhanced vasodilatation[17] and microvascular shunting, causing aggravation of symptoms.

Erythermalgia or erythromelalgia, although rare, is an important diagnostic consideration not only because erythromelalgia sometimes responds to aspirin but also to avoid potentially harmful treatment attempts provoked by excruciating pain. If left untreated erythromelalgia associated with myeloproliferative disorders may progress towards painful acrocyanosis and even peripheral gangrene.[18] Erythermalgia could resemble cellulitis, thrombophlebitis and other vaso-occlusive and inflammatory disorders. However, recognition of erythermalgia in fact is not difficult given the characteristic response of pain to cold.

As illustrated in this case, many doctors are not aware of this rare clinical syndrome. During a period of 14 months, our patient visited many specialists and underwent extensive diagnostic procedures and therapies, including invasive procedures such as chemical symphathectomy. Several drugs were added to the patient's medication without any improvement of symptoms. Conversely, the symptoms subsided after discontinuing verapamil. An important general lesson to be learned is to pay attention to a patient's medication before performing extensive diagnostic and therapeutic procedures. It should be appreciated that discontinuation of medication can also be used as a simple diagnostic test for clinical syndromes, such as erythermalgia.

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