

# Bone scan findings in erythromelalgia

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## Abstract

Erythromelalgia is a rare condition characterized by attacks of intensely painful, red and warm feet and/or hands. Symptoms typically are triggered by heat and relieved by cooling of the extremities. Primary cases are due to mutations in the gene for a sodium channel expressed in nociceptive and sympathetic ganglion neurons; secondary causes include blood disorders, infections, drugs, connective tissue diseases, neuropathic diseases, including diabetic neuropathy, and malignancies. We present bone scan findings in a case of erythromelalgia in an 18 years old student, in whom the symptoms developed suddenly. No underlying disease could be demonstrated and the patient fully recovered. The scan findings were strikingly similar to those of reflex sympathetic dystrophy.

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## Introduction

Erythromelalgia is a rare clinical condition, with an incidence of 1.3 per 100,000 reported in Olmsted County, Minnesota, USA [1], characterized by fluctuating erythema, warmth and swelling of the extremities accompanied by a sensation of intense burning pain [2-4]. It involves the feet and less frequently the hands. Symptoms typically are triggered by heat and relieved by cooling of the extremities. Primary cases are due to one of several mutations in the SCN9A gene which encodes an alpha subunit of the voltage gated Na(v)1.7 sodium channel expressed in nociceptive and sympathetic ganglion neurons. This mutation leads to overactivation of these neurons. Secondary causes of erythromelalgia include blood disorders, especially myeloproliferative disorders, infections, drugs, connective tissue diseases and vasculitis, neuropathic diseases, including diabetic neuropathy, gout, multiple sclerosis, thrombotic thrombocytopenic purpura and malignancies [2-4]. The physiopathology of this condition is variable, but centers around small fibre neuropathy [5-7] and alterations of microvascular blood flow [5, 8-10].

Here, we report a patient with a clinical diagnosis of erythromelalgia, in whom a three phase bone scan with <sup>99m</sup>Tc-oxidronate (HDP, hydroxymethylene diphosphonate) showed a pattern very similar to that of reflex sympathetic dystrophy of the right foot and to a lesser degree of the right hand. We endeavour to explain these findings in terms of the underlying physiopathology and in particular try and explain why the bone scan findings were lateralized in the face of more symmetrical symptoms and signs.

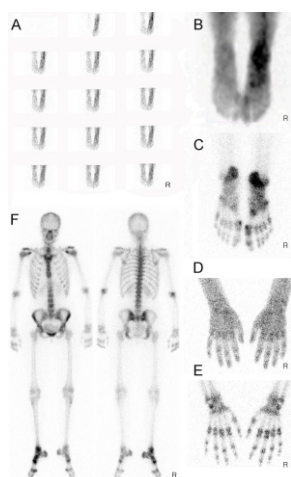
## Description of the Case

A 18 years old student without any significant medical history presented with a 2 weeks history of intermittent episodes of burning pain in the feet with swelling and erythema. The pain started when the patient stood waiting for a train in cold weather. Next day she had flu-like symptoms, which quickly recovered. One day later, she developed a burning sensation diffusely in the feet, which remained present intermittently, was highly increased by higher ambient temperature and for some days could be eased by cold. Swelling and erythema were present for some days. After some days, similar symptoms developed in the hands. Pain often was unbearable and little affected by painkillers and steroids, confining the patient to a wheelchair. Clinical examination revealed mild swelling and diffuse dysesthesia of the hands and feet. The sudomotor response, which measures the change of plantar or palmar epidermal resistance due to sweat gland activity after electric stimulation of the tibial or median nerve of the opposite limb, was absent in the left hand and decreased in the right foot.

Three phase bone scintigraphy (Figure 1) of the feet showed a strikingly increased tracer accumulation in the right foot and lower leg at both the vascular (panel A), blood pool (B) and bone phases (C, F). A less markedly increased tracer accumulation was also found in the right forearm and hand on the blood pool (D) and bone phases (E, F). The bone scan was thought suggestive of reflex sympathetic dystrophy of both the right foot and hand. Magnetic resonance imaging of the right foot, however, was normal, as was an arterial duplex of the affected limbs. Given the presence of a typical painful and fluctuating redness of the extremities, the clinical diagnosis of erythromelalgia was made. A mutation in the SCN9A gene could not be demonstrated using polymerase chain reaction (PCR) and sequence analysis.

A thorough workup including positron emission tomography/computed tomography (PET/CT) did not reveal any underlying disorder. Histologic examination of a skin biopsy taken after the bone scan on the extensor face of the middle phalanx of the left middle finger, was normal.

Pain management required the gamma-amino butyric acid analogue gabapentin (an inhibitor of voltage-dependent calcium channels) with the benzodiazepine clonazepam, both agents used in neuropathic pain, and the narcotic analgesic buprenorphin. Four months after the onset of complaints, the pain gradually subsided and the patient recovered completely.



**Figure 1.** Three phase bone scintigraphy with  $^{99m}\text{Tc}$ -oxidronate consisting of vascular (A) and blood pool phases of the feet (B), blood pool phases of the hands (D) and bone phases of the feet (C), hands (E) and whole body (F). A strikingly increased tracer accumulation was present in the right foot and lower leg at both the vascular (A), blood pool (B) and bone phases (C, F). A less markedly increased tracer accumulation was also found in the right forearm and hand on the blood pool (D) and bone phases (C, F). The patient's right side is marked by R. The bone scan was thought suggestive of reflex sympathetic dystrophy of both the right foot and hand, but the final clinical diagnosis was erythromelalgia.

## Discussion

To our knowledge this is the first report of bone scan findings in erythromelalgia. Although neither a SCN9A mutation nor an underlying disease could be demonstrated, this

does not preclude the clinical diagnosis, since even in some patients with inherited erythromelalgia no SCN9A pathogenic variant is identified [4].

In its early stages, reflex sympathetic dystrophy may be indistinguishable clinically from erythromelalgia [4, 5]; diminished vasoconstrictor responses have been found both in erythromelalgia and in reflex sympathetic dystrophy [8, 11, 12]. This may explain the similarity of the scintigraphic findings in these two conditions.

In the face of symmetric symptoms involving the feet and hands during an ongoing episode of erythromelalgia, it remains unclear why the bone scan abnormalities in our patient remained confined to the right side. However, in some patients the disease is unilateral [2, 5], and thermoregulatory sweat tests, which are a sensitive marker of the small nerve neuropathy that frequently is present in erythromelalgia, may show asymmetric patterns and do not always correlate with the location of the erythromelalgia, possibly because different nerve fibers are involved [13]. We hypothesize that in a similar fashion, bone scan alterations may not fully correlate with the extent of the erythromelalgia.

*In conclusion*, the  $^{99m}\text{Tc}$ -oxidronate bone scan findings in erythromelalgia, may mimic those of reflex sympathetic dystrophy, another painful condition with altered vaso-activity. Moreover, the extent of the bone scan abnormalities does not necessarily concur with the clinical involvement.

*The authors declare that they have no conflicts of interest.*

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