

## ONLINE FIRST

# Nonspecific Capillary Proliferation and Vasculopathy Indicate Skin Hypoxia in Erythromelalgia

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**Objective:** To report on the histopathologic findings of affected skin in consecutively collected biopsy specimens from 49 patients with erythromelalgia (EM).

**Design:** Skin biopsy specimens were obtained from the foot arch and analyzed by light microscopy, immunofluorescence microscopy, and electron microscopy.

**Setting:** Oslo University Hospital–Gaustad, University of Oslo, Oslo, Norway.

**Participants:** Thirty-one patients had primary EM, 17 patients had secondary EM, and 1 patient had erythromelalgic syndrome.

**Main Outcome Measure:** Evidence of microvascular abnormalities in skin biopsy specimens.

**Results:** Light microscopy showed evidence of capillary proliferation in 10 of 31 patients with primary EM and in 1 of 17 patients with secondary EM. The biopsy specimen from the patient with erythromelalgic syndrome showed numerous capillary nests with endothe-

lial cell defects and a slight perivascular inflammatory reaction. Among the 17 secondary EM cases, sparse perivascular lymphocyte infiltrations were observed in the biopsy specimens from 2 patients with chronic myelogenous leukemia and 1 patient with diabetes mellitus. Eleven patients also had signs of vasculopathy based on findings of immunodeposits of C3 and fibrin. Six of 30 patients with primary EM showed endothelial abnormalities on electron microscopy. All 3 investigations showed unremarkable biopsy results in 16 cases.

**Conclusions:** Histopathologic analysis is not useful as a routine diagnostic tool in EM because no morphological changes are specific to EM. The capillary proliferation and vasculopathy are assumed to be a consequence of intermittent skin hypoxia (vascular hypothesis of pathogenesis). Whether the proliferation is a consequence of EM or a pathogenic factor in the development of the disease is uncertain.

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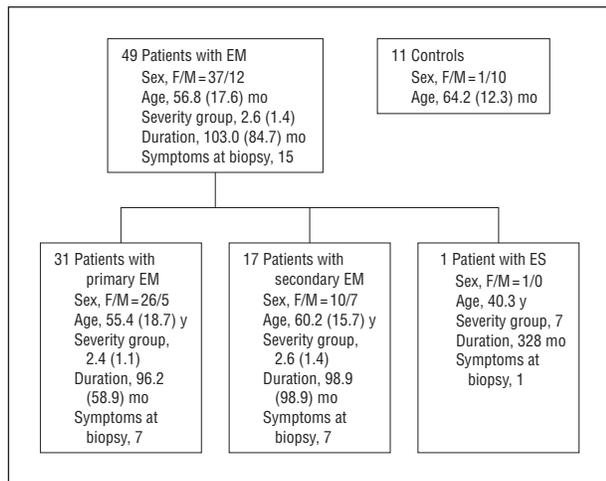
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**E**RYTHROMELALGIA (EM) IS A clinical syndrome that is characterized by erythema, increased skin temperature, and burning pain in the extremities. The pain is relieved by cooling and aggravated by warming.<sup>1</sup> It is commonly divided into primary and secondary cases,<sup>2</sup> depending on whether or not there is an underlying disease. A rare subtype, erythromelalgic syndrome (ES), which was described by Kvernebo,<sup>3</sup> has a strong hereditary component and usually affects the skin of the feet and legs. Some authors consider EM to be a symptom complex rather than a disease entity.<sup>3,4</sup> A clinical severity scale with 8 categories based on the need for cooling has been introduced for classification purposes.<sup>5</sup>

Knowledge about histopathologic findings in diseased skin of patients with EM is limited. Using light microscopy and immunohistochemical analysis, Davis et al<sup>6</sup> investigated 29 cases of primary EM and

found capillary alterations with hyperplasia, ectasia, endothelial swelling, or dermal fibrosis in a high proportion of biopsy specimens. These findings were considered to be nonspecific. A decrease in nerve ending density associated with dilated capillary loops was noted in 12 of 16 patients examined. Vascular thrombi were not identified. In addition to Davis and colleagues' study, we have found several other reports based on the histopathologic examination of 1 or more cases of EM, all of which demonstrated heterogenic and nonconclusive findings. Kvernebo<sup>3</sup> previously reported biopsy results from the skin of 6 patients with EM. Two specimens showed capillary proliferation, and 1 specimen showed cholesterol emboli, while 3 specimens showed no histopathologic findings.<sup>3</sup>

The pathogenesis of EM is debated. At present, some authors believe in a vasculogenic mechanism with maldistribution of microvascular perfusion through anatomical



**Figure 1.** Characteristics of the study participants. Severity group: Eight categories based on the need for cooling, where 0 indicates no symptoms and 8 indicates a continuous need for cooling or epidural anesthesia.<sup>5</sup> The values are expressed as mean (SD) unless indicated otherwise. EM indicates erythromelalgia; ES, erythromelalgic syndrome.

or functional microvascular arteriovenous shunts, with increased thermoregulatory perfusion and a relative lack of nutritive capillary perfusion in affected skin. The tissue consequently becomes hypoxic, causing supplying arterioles to dilate, which in turn leads to a paradoxical situation with the coexistence of hyperemia and hypoxia.<sup>3,4</sup> This hypothesis gives an explanation for why cooling universally reduces pain. The cooling reduces metabolism and thereby the hypoxia; the improvement of tissue oxygenation reduces the arteriolar dilatation; and hyperemia is less pronounced: the vicious cycle is reversed. Some authors believe that a primary neurogenic dysfunction of peripheral autonomous nerves induces a secondary maldistribution of perfusion with a microvascular shunt mechanism.<sup>7,8</sup>

In a previous study, Kalgaard et al<sup>9</sup> demonstrated the effect of infusion of prostacyclin on symptoms and on sympathetic dysfunction in EM. This drug acts by vasodilatation and inhibition of platelet activation, and our assumption is that the vasodilatory effect on precapillary sphincters increases nutritive skin perfusion. Another study demonstrated that the prostaglandin E1 analogue misoprostol reduces symptoms and microvascular arteriovenous shunting in EM.<sup>10</sup> According to the vascular hypothesis, affected skin is hypoxic during attacks. Since hypoxia is known to be a strong stimulus for angiogenesis,<sup>11</sup> findings of microvascular proliferation in affected skin of patients with EM would support the hypothesis of a vascular pathogenetic mechanism. To our knowledge, this article represents the first report to describe the histopathologic changes in consecutively collected skin biopsy specimens from patients with EM examined by light microscopy, immunofluorescence (IF) microscopy, and electron microscopy.

## METHODS

### STUDY POPULATION

Since 1983, we have collected a database of cases of EM, and a review of the clinical and epidemiological characteristics in 87

cases has previously been reported.<sup>5</sup> In the present prospective study, all patients in the database with EM symptoms were invited to participate, and 49 patients who were eligible for inclusion agreed. We also included 1 female patient without symptoms at the time of examination. She had previously had a limb-threatening case of EM and had been treated successfully with prostaglandin E1.<sup>3</sup> Therefore, 50 patients, along with 11 controls, were included in the study (**Figure 1**).

When biopsy specimens were obtained, the patients' symptoms were recorded according to a clinical severity scale based on the need for cooling.<sup>5</sup> The duration of disease and patient age and sex were also recorded. The controls were healthy volunteers. Informed written consent was obtained from all patients. The study was approved by the regional ethical committee.

### BIOPSY PROCEDURE

Fifty boat-shaped excision biopsy specimens measuring 1.5 × 0.5 cm were obtained from the medial arch of the sole of the foot of the patients and the controls. In 1 case of EM in which only the hands were affected, the biopsy specimen was obtained from the palm. One patient with ES, described previously in detail,<sup>3</sup> had a total 3 of biopsy specimens obtained on different occasions and from different locations: from the plantar aspect of the foot, from the dorsal aspect of the foot, and from the amputated right leg.

All biopsy specimens were divided into 3 equal parts: 1 for light microscopy, 1 for IF microscopy, and 1 for electron microscopy. One biopsy specimen was excluded from analysis because it contained only epidermis, leaving biopsy specimens from 49 patients for examination. Furthermore, in 1 of the 31 cases of primary EM that was prepared for electron microscopy, the material was accidentally destroyed, which left 30 primary EM cases for the electron microscopic investigation.

### LIGHT MICROSCOPY

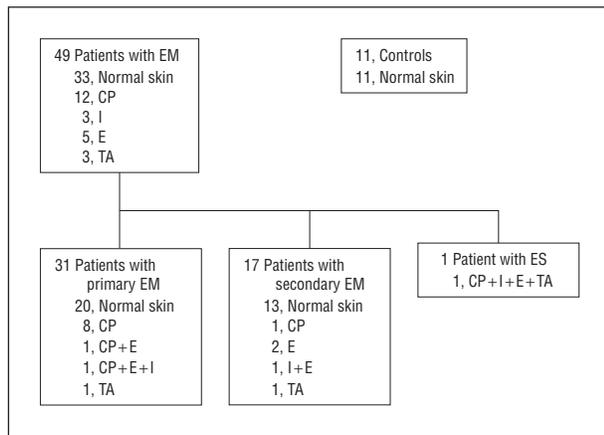
The biopsy specimens were fixed in formalin and embedded in paraffin and processed for routine histopathologic evaluation by light microscopy. Sections were cut at a thickness of 5 μm and stained with hematoxylin-eosin for routine examination. When the histopathologic changes were reported, special emphasis was paid to vascular density and capillary formation as well as possible edema and inflammation.

### IF MICROSCOPY

The biopsy specimens were quick frozen in embedding medium (Tissue-Tek OCT [optimal cutting temperature] Compound; Laboratory-Tek Products Division, Miles Laboratories, Naperville, Illinois) and stored at -70°C until use. Frozen sections were then examined with direct IF using the following specific antibodies labeled with fluorescein isothiocyanate: anti-Fc IgG (Behringwerke, Marburg, Germany), anti-Fc IgA (Behringwerke), anti-C3c (Behringwerke), antifibrinogen/antifibrin (Behringwerke), and anti-Fc IgM (Dakopatts, Glostrup, Denmark). The IF microscopic examinations were performed with an incident light microscope (Leitz Orthoplan; Leica Mikrosysteme Vertrieb GmbH, Mikroskopie und Histologie, Wetzlar, Germany).

### ELECTRON MICROSCOPY

The specimens were fixed by immersion in buffered 0.1M phosphate buffer (pH, 7.4) containing 2.5% glutaraldehyde and post-fixed in 1% osmium tetroxide in 0.1M cacodylate buffer. They



**Figure 2.** Light microscopy results. CP indicates capillary proliferation; E, edema; EM, erythromelalgia; ES, erythromelalgic syndrome; I, inflammation; and TA, thickened arteries.

were dehydrated in ethanol and embedded in Epon 812. Semi-thin sections were stained with toluidine blue, and ultrathin sections were stained with uranyl acetate–lead citrate and examined with an electron microscope (JEOL 100B; JEOL Ltd, Tokyo, Japan).

## STATISTICAL ANALYSIS

Statistical analyses were performed with statistical software (Statview SE+ Graphics; Abacus Concepts Inc, Piscataway, New Jersey). Comparison between groups were performed using the Mann-Whitney *U* test, and differences were considered significant at  $P < .05$ .

## RESULTS

Sixteen of our 49 patients had normal findings with all 3 investigational techniques.

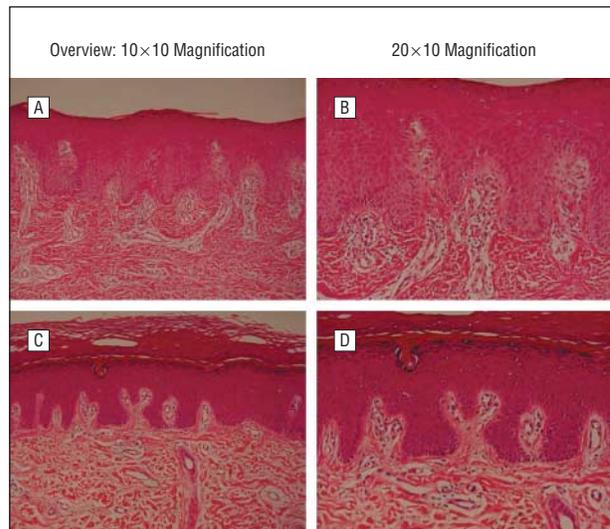
### LIGHT MICROSCOPY

Of 49 EM biopsy specimens, 33 did not show pathologic findings. Of the remaining 16 specimens, 12 showed increased numbers of capillary profiles in the papillary dermis compared with control biopsy specimens (**Figures 2, 3, and 4**). Other findings were inflammation, edema, and thickened arteries (Figure 2). Vasculitis or thrombosis were not found in any of the biopsy specimens.

The disease severity of the 12 patients with capillary proliferation was not different from that of the remaining 37 patients without proliferation (2.5 vs 2.9 on a severity scale of 8 categories;  $P = .85$ ). The mean duration of the disease was 98.1 months for patients with proliferation vs 104.8 months for patients without proliferation ( $P = .87$ ).

### IF RESULTS

Twenty-eight specimens showed no abnormalities, whereas the remaining 21 specimens had pathologic deposits (**Figure 5**). The deposits were found in the walls of small vessels. C3c and immunoglobulins were seen as granular



**Figure 3.** Histopathologic features of primary erythromelalgia (EM). Biopsy specimens from the medial aspect of the arch of the sole of the foot of 2 patients with primary EM. Epidermis with a cornified layer is typical for the region. Note the increased number of capillaries in the papillae (hematoxylin-eosin, original magnification  $\times 100$  [A and C] and original magnification  $\times 200$  [B and D]).

or small lumpy deposits, while fibrin was usually seen more diffusely in the inner part of the vessel wall.

The combination of complement and fibrin deposits in vascular walls is consistent with vasculopathy in terms of IF microscopy and indicates damage to vessel walls. It may be seen along with vasculitis but is not diagnostic for this condition. None of these patients, or any other patients, had signs of vasculitis according to clinical or light microscopic findings. Three of 12 patients with capillary proliferation vs 8 of 37 without such a finding had IF deposits of complement and fibrin in small-vessel walls. Immunofluorescence showed vasculopathy deposits in vessel walls in 8 of 31 patients with primary EM and in the 1 patient with ES vs 2 of 17 patients with secondary EM ( $P = .44$ ).

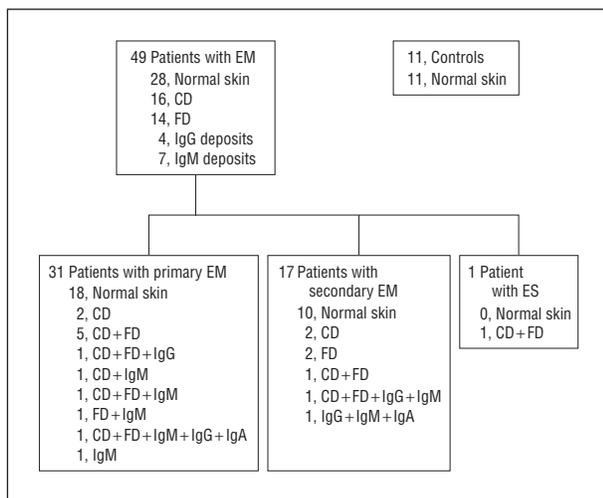
The severity and duration of EM did not correlate with the finding of vasculopathy. The mean disease severity for the 11 patients with EM and vasculopathy was 2.6 vs 2.7 for the 38 patients without vasculopathy ( $P = .75$ ). The mean duration of disease for the 11 patients with EM and vasculopathy was 97.2 months vs 108.0 months for the 38 other patients ( $P = .92$ ). The specimen from the patient with ES showed deposits of C3 and fibrin in dermal vessels, suggestive of damage to the vessel walls, but light microscopy did not show vasculitis.

### ELECTRON MICROSCOPY

Forty-eight biopsy specimens from patients with EM were examined. Six of 30 patients with primary EM showed endothelial abnormalities demonstrated as either endothelial cell defects or swollen endothelium, with or without perivascular leukocyte accumulation. One specimen from a patient with primary EM showed only perivascular leukocyte infiltration, without endothelial cell defects. Of the 7 cases involving endothelial cell abnormalities with or without swelling of endothelial cells,



**Figure 4.** Three biopsy specimens were obtained from the patient with hereditary erythromelalgic syndrome—1 in 1983, 1 in 1991, and 1 from the amputated right leg in 1993—and stained with hematoxylin-eosin. A, The patient's legs and feet in 1983. B, The biopsy specimen shows increased numbers of small vessels in papillary dermis, mainly clustered in small groups, and there are dilated small vessels deeper in the corium and subcutis (original magnification  $\times 200$ ). C, The patient's left foot in 1991. D, The biopsy specimen shows epidermal spongiosis and dilated and increased numbers of capillaries in the dermis, with papillary edema and some lymphomonocytic cells in the deeper layers (original magnification  $\times 100$ ). E, The patient's legs and feet in 1993. F, The top part of the biopsy specimen from the amputated foot shows epidermal hyperplasia with a large area of fibrosis in a very broadened dermis (original magnification  $\times 20$ ). G, The bottom part of the specimen shows hyperplastic epidermis and dermal papillae with increased number of vessels, edema, fibrosis, and mild inflammation (original magnification  $\times 100$ ).



**Figure 5.** Immunofluorescence results. CD indicates complement deposits; EM, erythromelalgia; ES, erythromelalgic syndrome; and FD, fibrin deposits.

6 were found in specimens with capillary proliferation demonstrated by light microscopy. Sparse perivascular lymphocyte infiltration, which was observed in the specimens from 2 patients, was the only significant morphological change seen among the 17 secondary EM cases; one patient had chronic myelogenous leukemia, and the other had diabetes mellitus. The ES case showed numerous capillary nests with endothelial cell defects and slight perivascular inflammatory reaction.

#### COMMENT

Since 1983, in Norway, a nation of 4.6 million inhabitants, we have been able to collect a database of patients with EM. To a great extent, the patients were referred from general practice and dermatology colleagues who

were familiar with our interest in this condition. When the patients of the present study were recruited, the database comprised 87 patients, and all live patients were invited to participate. A detailed presentation of the clinical findings has previously been published.<sup>5</sup> The present study did not reveal specific diagnostic findings in skin biopsy specimens. Capillary proliferation or vascular damage was demonstrated in 31 of 49 specimens, mainly in those from patients with primary EM.

#### THE VASCULOGENIC HYPOTHESIS OF EM

Capillary proliferation was observed in 10 of 31 patients with primary EM and in only 1 of 17 patients with secondary EM. The ES case had marked nests of proliferated capillaries (Figure 4). It is well known that the architecture of the capillary network is dynamically adapting to functional demands. Angiogenesis, eg, is an essential part of cancer growth, claudication, and angina pectoris.<sup>12</sup> During systematic exercise, muscle capillary density is increasing, and the stimulus to growth is believed to be local hypoxia.<sup>13</sup> Hypoxia may also be a stimulus for capillary proliferation in the skin.<sup>11</sup> The term *skin hypoxia* usually refers to an anatomical skin area, but skin hypoxia can also be caused by systemic microvascular disturbances, such as diabetes microangiopathy and sepsis, or by local microvascular disturbances, such as microemboli and thromboses. August Krogh<sup>14</sup> was awarded the Nobel Prize in physiology and medicine in 1920. One of his achievements was the identification of the "Krogh cylinder," postulating that all cells need to be located within a critical radius of a perfused capillary to survive. The radius of the cylinder is defined by the limited diffusion capacity of oxygen in the tissue, and cells located outside such a radius will experience insufficient nutrition. In tissues with a large heterogeneity of distribution of perfused capillaries, some cells will experience low

oxygen tension, while cells that are near to perfused capillaries will experience adequate oxygen tension. Microvascular perfusion is dynamically regulated and varies with time owing to neuroendocrine and paracrine factors giving rise to temporal variation in local perfusion. We have postulated that in patients with EM and stable central hemodynamic and open arteries, the skin becomes intermittently hypoxic, with attacks of shunting through anatomical arteriovenous anastomoses located in the skin of the hands and feet.<sup>3,15</sup> Our prestudy hypothesis was therefore that we would find capillary proliferation in the skin because of hypoxia as a stimulus for microvascular proliferation.

In the biopsy specimen from the patient with ES, we found nests of capillaries, atrophy of adnexal skin structures, and hyperplastic epidermis. Skin atrophy may be a consequence of the patient's chronic hypoxia of the skin, which was documented on several occasions by extremely low levels of transcutaneous oxygen tension and an inability to heal an ulcer in spite of open leg arteries and normal deep venous function.<sup>3</sup>

Of the 31 patients with primary EM, 10 had capillary proliferation, but none had atrophy of the adnexal structures. Hypoxia in EM is also documented by previous reports showing skin necrosis leading to leg amputation in 2 patients with EM and open leg arteries<sup>5</sup> and by a case involving an 8-year-old girl with nail growth disturbances during 3 months of acute severe EM and extremely low levels of transcutaneous oxygen tension.<sup>3</sup>

Capillary proliferation was not found in 37 of 49 patients, and we did not find any correlation with duration or severity of EM. It is uncertain why only some patients develop proliferation. It is possible that proliferation is the result of a complex interaction between cytokines, progenitor cells, and hypoxia and that patients with EM have different genetic capacities for microvascular angiogenesis.

We consider the abnormal IF findings in patients without clinical and light microscopic findings of vasculitis to represent vascular damage that could be termed vasculopathy. This could be induced by hypoxia. The clinical observation that the use of prednisolone and nonsteroidal anti-inflammatory agents is generally of little therapeutic value in EM is consistent with the relatively few signs of inflammation observed. The electron microscopy findings in 7 cases with either absence or swelling of endothelial cells are also consistent with the hypoxia hypothesis.

Apart from the study by Davis et al,<sup>6</sup> all previously published reports of skin abnormalities in EM have involved selected materials from a few patients, mainly ones who were recruited from a hematology practice.<sup>16-18</sup> Capillary proliferation has previously been reported by Monk et al<sup>19</sup> in 1 case, by Kvernebo<sup>3</sup> in 2 cases, and by Davis et al<sup>6</sup> in 18 cases. In contrast to a few cases reported elsewhere,<sup>16-18</sup> we found no cases with microthrombi.

In patients with EM secondary to thrombocytopenia and chronic myeloid leukemia, histopathologic analysis has shown arteriolar changes with swollen and large nuclei and narrowing of the lumen caused by fibromuscular and intimal arteriolar proliferation and occluding

thrombi.<sup>16-18</sup> Monk et al<sup>19</sup> found marked focal capillary proliferation in the upper dermis and a minimal inflammatory infiltrate in a patient with EM secondary to pergolide administration for Parkinson disease.<sup>19</sup> Eisler et al<sup>20</sup> examined 3 patients with EM-like eruptions due to the use of bromocriptine. Prominent perivascular lymphocyte infiltration and perivascular edema of the dermis, without vasculitis, were found. Symptoms and histopathologic findings were reversible when the therapy was discontinued. These reports are all compatible with our vascular pathogenetic hypothesis of EM.

## THE NEUROGENIC HYPOTHESIS OF EM

Over the last years, a neurogenic hypothesis for the pathogenesis of EM has been presented, but in this study, we did not examine the density of autonomic nerves in the skin. Uno and Parker<sup>21</sup> showed the degeneration of autonomic nerve plexuses in affected skin of 1 patient with EM, and the results were compared with unaffected skin of the same individual and with the skin of a control person. Blanchard et al<sup>22</sup> showed a slight and questionable reduction in the density of autonomic adrenergic nerve terminals in the periarterial and glandular plexuses in the skin of 1 patient. The finding of decreased nerve fiber density associated with dilated capillary loops in 12 of 16 patients with primary EM described by Davis et al<sup>6</sup> supports the hypothesis that patients with primary EM may have a small-fiber neuropathy. In electrophysiologic studies, Ørstadvik et al<sup>7,8</sup> have demonstrated small, afferent, nerve fiber dysfunction in patients with EM. Several authors have demonstrated that primary, hereditary EM may be a neuropathic disorder of small sensory and sympathetic neurons caused by a genetic defect in the gene *SCN9A*, which codes for NaV1.7, a sodium channel in peripheral thin-fiber neurons. The defect leads to hyperexcitability of sensory small-fiber neurons and reduced lidocaine sensitivity.<sup>23-25</sup>

In our biopsy study, we were not able to study nerve endings. However, in our opinion, there is no conflict between the vascular and the neurogenic hypothesis. We believe that a primary thin-fiber dysfunction can lead to a secondary vascular maldistribution and hypoxia accompanied by secondary capillary proliferation and, vice versa, that a primary vascular maldistribution leading to skin hypoxia can cause a secondary hypoxic-induced neuropathy.

In summary, no specific diagnostic findings were demonstrated in skin biopsy specimens from patients with EM. Capillary proliferation was seen in 12 of 49 patients, and vasculopathy with immunodeposits of C3 and fibrin was seen in 11 patients. The vascular and neuropathic hypotheses of pathogenesis are not mutually exclusive, as arterioles, shunts, and venules are partially under neurologic control. The findings are compatible with the prestudy hypothesis that recurrent episodes of skin hypoxia in selected patients may lead to microvascular damage followed by vascular proliferation.

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**Author Contributions:** Drs Kalgaard and Kvernebo had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Kalgaard and Kvernebo. *Acquisition of data:* Kalgaard and Kvernebo. *Analysis and interpretation of data:* Kalgaard, Clausen, Mellbye, Hovig, and Kvernebo. *Drafting of the manuscript:* Kalgaard, Clausen, Mellbye, Hovig, and Kvernebo. *Critical revision of the manuscript for important intellectual content:* Kalgaard, Clausen, Mellbye, Hovig, and Kvernebo. *Statistical analysis:* Kalgaard and Kvernebo. *Obtained funding:* Kalgaard and Kvernebo. *Administrative, technical, and material support:* Kalgaard, Clausen, Mellbye, Hovig, and Kvernebo. *Study supervision:* Kvernebo.

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## REFERENCES

1. Thompson GH, Hahn G, Rang M. Erythromelalgia. *Clin Orthop Relat Res.* 1979; 144(144):249-254.
2. Smith LA, Allen EV. Erythromelalgia (erythromelalgia) of the extremities: a syndrome characterized by redness, heat, and pain. *Am Heart J.* 1938;16:175-188.
3. Kvernebo K. Erythromelalgia: a condition caused by microvascular arteriovenous shunting. *Vasa.* 1998;51(suppl):1-39.
4. Mørk C, Kvernebo K. Erythromelalgia—a mysterious condition? *Arch Dermatol.* 2000;136(3):406-409.
5. Kalgaard OM, Seem E, Kvernebo K. Erythromelalgia: a clinical study of 87 cases. *J Intern Med.* 1997;242(3):191-197.
6. Davis MD, Weenig RH, Genebriera J, Wendelschafer-Crabb G, Kennedy WR, Sandroni P. Histopathologic findings in primary erythromelalgia are nonspecific: special studies show a decrease in small nerve fiber density. *J Am Acad Dermatol.* 2006;55(3):519-522.
7. Ørstavik K, Weidner C, Schmidt R, et al. Pathological C-fibres in patients with a chronic painful condition. *Brain.* 2003;126(pt 3):567-578.
8. Orstavik K, Mørk C, Kvernebo K, Jørum E. Pain in primary erythromelalgia—a neuropathic component? *Pain.* 2004;110(3):531-538.
9. Kalgaard OM, Mørk C, Kvernebo K. Prostacyclin reduces symptoms and sympathetic dysfunction in erythromelalgia in a double-blind randomized pilot study. *Acta Derm Venereol.* 2003;83(6):442-444.
10. Mørk C, Salerud EG, Asker CL, Kvernebo K. The prostaglandin E1 analog misoprostol reduces symptoms and microvascular arteriovenous shunting in patients with erythromelalgia: a double-blind, crossover, placebo-compared study. *J Invest Dermatol.* 2004;122(3):587-593.
11. Ryan TJ. The blood vessels of the skin. *J Invest Dermatol.* 1976;67(1):110-118.
12. Nishida T. Angiogenesis, which is essential for cancer growth, is a diagnostic and therapeutic target. *J Gastroenterol.* 2005;40(3):320-321.
13. Richardson RS, Wagner H, Mudaliar SR, Henry R, Noyszewski EA, Wagner PD. Human VEGF gene expression in skeletal muscle: effect of acute normoxic and hypoxic exercise. *Am J Physiol.* 1999;277(6, pt 2):H2247-H2252.
14. Krogh A. *Nobel Lecture in Physiology and Medicine 1920: Nobel Lectures, Physiology and Medicine 1901-1921.* Amsterdam, the Netherlands: Elsevier Publishing Co; 1967.
15. Mørk C, Kvernebo K, Asker CL, Salerud EG. Reduced skin capillary density during attacks of erythromelalgia implies arteriovenous shunting as pathogenetic mechanism. *J Invest Dermatol.* 2002;119(4):949-953.
16. Michiels JJ, ten Kate FW, Vuzevski VD, Abels J. Histopathology of erythromelalgia in thrombocythaemia. *Histopathology.* 1984;8(4):669-678.
17. Croue A, Gardembas-Pain M, Verret JL, Boasson M, Rousselet MC, Saint Andre JP. Histopathologic lesions in erythromelalgia during essential thrombocythemia [in French]. *Ann Pathol.* 1993;13(2):128-130.
18. Kurzrock R, Cohen PR. Erythromelalgia and myeloproliferative disorders. *Arch Intern Med.* 1989;149(1):105-109.
19. Monk BE, Parkes JD, Du Vivier A. Erythromelalgia following pergolide administration. *Br J Dermatol.* 1984;111(1):97-99.
20. Eisler T, Hall RP, Kalavar KA, Calne DB. Erythromelalgia-like eruption in parkinsonian patients treated with bromocriptine. *Neurology.* 1981;31(10):1368-1370.
21. Uno H, Parker F. Autonomic innervation of the skin in primary erythromelalgia. *Arch Dermatol.* 1983;119(1):65-71.
22. Blanchard P, Grenier B, Marchand S, Ruchoux MM. Erythromelalgia, arterial hypertension and increased excretion of urinary catecholamines [in French]. *Arch Fr Pediatr.* 1987;44(9):799-802.
23. Michiels JJ, te Morsche RH, Jansen JB, Drenth JP. Autosomal dominant erythromelalgia associated with a novel mutation in the voltage-gated sodium channel alpha subunit Nav1.7. *Arch Neurol.* 2005;62(10):1587-1590.
24. Sheets PL, Jackson JO II, Waxman SG, Dib-Hajj SD, Cummins TR. A Nav1.7 channel mutation associated with hereditary erythromelalgia contributes to neuronal hyperexcitability and displays reduced lidocaine sensitivity. *J Physiol.* 2007; 581(pt 3):1019-1031.
25. Waxman SG. Nav1.7, its mutations, and the syndromes that they cause. *Neurology.* 2007;69(6):505-507.