Histopathological findings in primary erythromelalgia show a decrease in small nerve fiber density.

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The histopathology of primary erythromelalgia has been poorly characterized. A total of 33 skin biopsy specimens from 29 patients with a diagnosis of primary erythromelalgia were re-examined. Histopathologic findings were nonspecific. Vascular thrombi were not identified. A relative decrease in small nerve fiber density was noted in specimens from 13 of 16 patients. (J Am Acad Dermatol 2006;55:519-22.)

Erythromelalgia, initially described more than a century ago,[1,2] is a rare clinical syndrome defined by intermittent or continuous flushing of acral areas such as the feet and hands. The flushing is associated with heat and discomfort, which are often severe to the point of being disabling.[3] To emphasize the importance of heat (‘‘thermos’’),

it has been proposed that the condition be called ‘‘erythermalgia.’’ The diagnosis of erythromelalgia as a clinical syndrome is dependent on a clinical history and

physical examination. Laboratory tests may support the diagnosis of erythromelalgia or document the severity of the disease; such tests include noninvasive vascular testing and a comparison of local skin temperature, blood flow, and transcutaneous oximetry

measurements in the symptomatic versus the asymptomatic state.[4,5] However, these tests are not generally available. In skin biopsy specimens from patients with secondary erythromelalgia secondary to myeloproliferative disease, thrombi are observed in small

arteries and arterioles.[6] However, very few descriptions exist of biopsy findings in primary erythromelalgia. We, therefore, examined the histopathologic findings of skin biopsy specimens from patients with confirmed primary erythromelalgia.

Table I. Characteristics and test results of patients with primary erythromelalgia

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Characteristic/test result	Patients (N = 29)
Mean age, y (range)	53 (21-96)
Women	23
Site of involvement	
Feet/lower extremities	27
Hands	10
Face	5
Vascular studies performed	22
Erythromelalgia confirmed	15
Neurophysiologic testing performed	22
EMG	
Normal	12
Abnormal	6
Autonomic nerve testing	
Normal	5
Abnormal	17
QSART	
Normal	6
Abnormal	16
Adrenergic function testing	
Normal	20
Abnormal	2
Thermoregulatory sweat testing	
Normal	3
Abnormal	8
Cardiovagal function	
Normal	7
Abnormal	4

Values are number of patients unless otherwise stated. EMG, Electromyography; QSART, quantitative sudomotor axon reflex test.

METHODS

Definition of primary erythromelalgia

Primary erythromelalgia was defined as the occurrence of erythema, heat (observed subjectively and objectively), associated discomfort (variously described as pain, burning, tingling, or a similar sensation) in the extremities, and absence of a recognized

secondary cause such as myeloproliferative disease.

Patients

This study was approved by our institutional review board. Our patient database was retrospectively searched for the records of patients fulfilling the criteria for the diagnosis of primary erythromelalgia who had undergone skin biopsy of the affected area between 1978 and January 2005; 29 patients were identified. All patients were white with a mean

age of 53 years (range: 21-96 years). Their demographic characteristics are summarized in Table I. No problems with healing after the biopsies were noted.

Skin biopsy specimens

Skin biopsy specimens from the patients were retrieved for re-evaluation. A total of 33 biopsy specimens were obtained from the 29 patients; most (25 specimens) had been taken between 2000 and January 2005. The biopsy specimens (one or two 3- to 5-mm punch biopsy specimens/patient) were obtained from the site or sites at which symptoms

occurred (eg, feet, hands, toes, or fingers). All but two of the biopsy specimens were from the lower extremities. All biopsy specimens were formalin fixed and paraffin embedded, then hematoxylineosin stained at the time they were taken. All stained biopsy specimens were examined by a board-certified dermatopathologist and dermatologist (R. H. W.

and M. D. P. D.). Between January 2004 and January 2005, part of each biopsy specimen was sent directly for nerve studies as described below.

Examination of nerves in biopsy specimens

Nerve fibers were examined and quantified as previously described.7 Biopsy specimens being processed for nerve fiber analysis by confocal microscopy were fixed in Zamboni's fixative for 24 hours then transferred to sucrose. Some of the formalinfixed specimens were also deparaffinized and stained for nerve studies.2 To ensure that the process of deparaffinization did not induce artifact, two of the most recently harvested specimens were processed with both techniques for comparison. The two specimens were cut*e*half was formalin fixed then put in paraffin and subsequently deparaffinized, and the other half was fixed in Zamboni's fixative. A detailed description of the technique has been reported previously.8,9

The fixed specimens were then stained with primary antibody against panneuronal marker for nerves and protein gene product 9.5 (Ultraclone Ltd,Wellow, United Kingdom), combined with antibodies to either panendothelial marker CD31 (DakoCytomation, Carpinteria, Calif) or type IV collagen (Chemicon International Inc, Temecula, Calif). Cyanine fluorophores 2 and 3 were subsequently applied for visualization. Specimens were initially examined with a epifluorescence microscope (Nikon, Melville, NY). The sections were then imaged with an MRC-1000 scanning confocal microscope system equipped with a Kr/Ar ion laser (Bio-Rad Life Science, Hercules,Calif). A series of sections (320 magnification) was acquired at 2-_m intervals through the entire thickness of each specimen (approximately 30 _m) and then projected into a single-focus image with the software supplied (Confocal microscope, Atto

Biosciences, Rockville, Md) to generate a tridimensional image. We then counted nerve fibers and measured the diameter of the capillary loops. The deparaffinized and Zamboni-fixed halves of the two control slides were then compared; no significant difference in the

nerve fiber count or the morphology was noted. Therefore, we believed that the results from the other deparaffinized biopsy specimens would be reliable, and we used the data from all the samples regardless of their preparation.

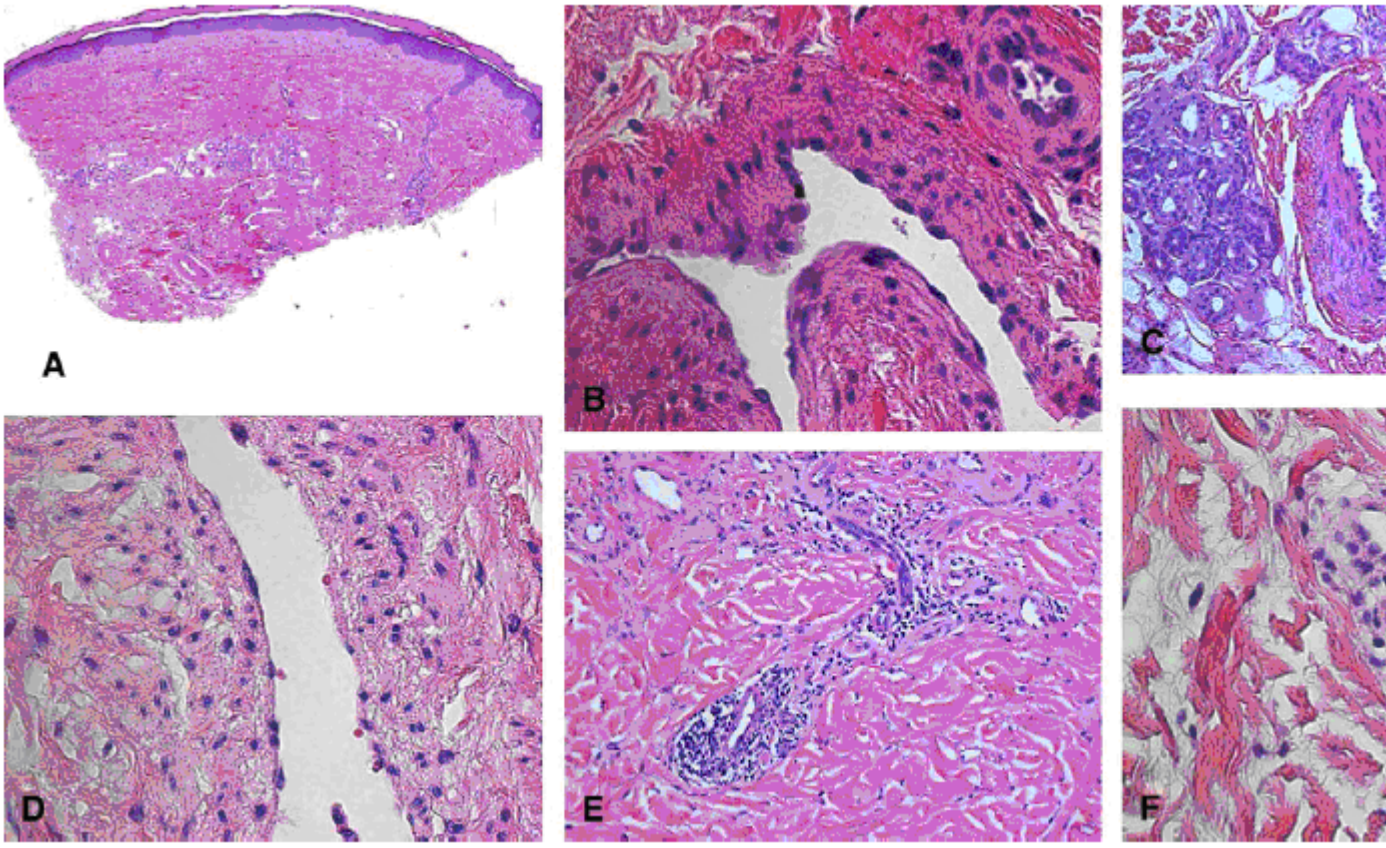

Fig 1. Histopathology of skin biopsy specimens. A, Low-power view of specimen from back of foot of patient with erythromelalgia showing perivascular lymphocytic inflammation and perivascular edema. B, Arteriolar endothelial cell swelling and nuclear enlargement. C, Arteriolar smooth-muscle hyperplasia. D, Intracellular edema and vacuolar changes of arteriolar smooth-muscle cells. E, Perivascular lymphocytic inflammation. F, Perivascular edema. (A to F, Hematoxylin-eosin stain; original magnifications: A,325; B and D,3630; C and E, 3200; F, 3400.)

RESULTS

A representative low-power view of a skin biopsy specimen from the back of the foot of one of the patients is shown in Fig 1, A. Results of the histopathologic evaluation were obtained from the 33 skin biopsy specimens. Vascular thrombi were not identified in any of the specimens. Of the 33 specimens examined, mild dermal fibrosis was noted in

18 (55%), endothelial swelling in 22 (67%), nuclear enlargement in 24 (73%) (Fig 1, B), capillary hyperplasia in 18 (55%), and capillary ectasia in 12 (36%).

The biopsy specimens sampled arterioles in 23 specimens. Smooth-muscle cell hyperplasia was noted in 20 (87%) (Fig 1, C), swelling in 18 (78%), and vacuolization in 1 (4%) (Fig 1, D). The arteriolar basement membrane was thickened in 15 (65%).

Fibrosis of arterioles was observed in 3 (13%), with laminar fibrosis observed in 2 (9%).

Perivascular lymphocytic inflammation was present in 24 (73%) (Fig 1, E), which was minimal to mild in 23 and dense in 1. Perivascular edema (Fig 1, F) was noted in 17 specimens (52%), which was minimal to mild in 15 and moderate in 2. In all, 21 biopsy specimens from 16 patients were processed for nerve fiber density estimation. The

epidermal nerve fiber count was lower than normal (ie, the count was below the fifth percentile for each specific site) in 13 of 16 patients (81%) (Fig 2), which is consistent with small fiber neuropathy. Axonal swellings (suggestive of early axonal damage) were

relatively few compared with the incidence in other neuropathies. Similarly, no evidence of excessive nerve terminal branching was found, as is typically observed in regenerating nerve fibers. Decreased nerve fiber density associated with dilated capillary loops was present in 12 of 16 patients. A biopsy specimen from an unaffected site showed normal nerve fiber density.

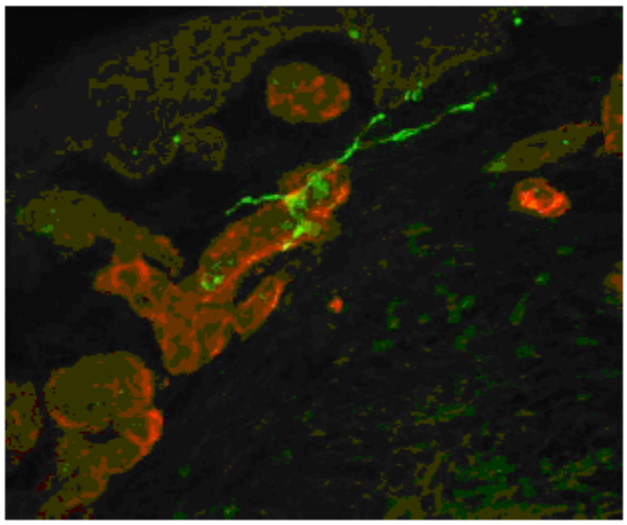

Fig 2. Confocal microscopic image of biopsy specimen stained for nerves with antibodies to protein gene product 9.5 (green) combined with antibodies to panendothelial marker CD31 (red). Epidermal and perivascular nerve fibers surrounding blood vessels are decreased in density. (Original magnification 3400.)

DISCUSSION

We present the biopsy findings of 29 patients with primary erythromelalgia. The largest series to date of patients with primary erythromelalgia is the study of 3 patients by Drenth et al.[10] In contrast to the reported histologic findings in secondary erythromelalgia,[11,12] thrombi were not observed. The presence of thrombi in secondary erythromelalgia may explain why these patients often respond to antiplatelet agents such as aspirin, whereas patients with primary erythromelalgia usually do not respond to such therapy. The pathogenesis of primary erythromelalgia may be different from that of secondary erythromelalgia. In general, the histopathologic findings observed in primary erythromelalgia in our study were nonspecific and pertained to changes in or around blood vessels; these changes may also be observed in venous hypertension, chronic edema, or may even be within normal limits. Thus, from a clinical standpoint,

skin biopsies were not useful in ascertaining the diagnosis or planning treatment. Similar histologic findings have been reported in drug-induced erythromelalgia.[13,14]

Our current morphologic observations that epidermal nerve density was decreased in 81% of the patients evaluated support our previous reports that, functionally, patients with erythromelalgia have a small fiber neuropathy.[4,5] Indeed, many of the patients

included in this study did have a functional small fiber neuropathy, which was primarily seen as a defect in the mechanism of sweating as evaluated by the quantitative sudomotor axon reflex test (Table I).

In conclusion, the biopsy specimens obtained from patients with primary erythromelalgia showed relatively subtle and nonspecific histologic findings. Importantly, no intraluminal occlusions or thrombi were noted, in contrast to previous reports of biopsy

specimens from patients with erythromelalgia secondary to myeloproliferative disease. Epidermal and perivascular nerve density was decreased in the biopsy specimens studied, which is consistent with neurophysiologic studies indicating neuropathy in these and other patients with primary erythromelalgia.

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