

Cutaneous Pathology in Primary Erythermalgia

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Primary or idiopathic erythermalgia is characterized by recurrent, red, warm, and painful lower extremities. It arises at young age and persists throughout life because no treatment is available. We report the cutaneous pathology of affected skin lesions of three patients with primary erythermalgia. Biopsy specimens showed a mild perivascular mononuclear infiltrate, thickened blood vessel basement membranes, abundant perivascular edema, and moderate endothelial swelling. The thickened basal membrane of the blood vessels showed a laminar structure, and abundant perivascular edema and moderate endothelial cell swelling were evident. These histopathologic findings in primary erythermalgia appear to be nonspecific but allow diagnostic differentiation from erythromelalgia in which fibromuscular intimal proliferation and occlusive thrombi in the endarteriolar capillaries are apparent and from erythermalgia secondary to vasculitis. Histopathologic examination of affected skin lesions in patients with red, congested, warm, and painful burning extremities is a valuable tool in the diagnostic process.

Key Words: Primary—Erythermalgia—Histopathology—Skin.

Erythromelalgia and erythermalgia are defined as two independent and completely different disease entities (1-3). Clinically, there are three different types of recurrent red, warm, and burning pain in the extremities. Erythromelalgia is closely associated with thrombocythemia ($\geq 350 \times 10^9/L$) in its primary form or is associated with various chronic myeloproliferative disorders (4,5). Symptoms are caused by platelet activation and aggregation in the end-arteriolar circulation, leading to ischemia and symptoms. The long-lasting relief of burning distress for 2-4 days afforded by a single low dose of aspirin is the valuable diagnostic test for erythromelalgia (6). The histopathology of erythromelalgia comprises arteriolar changes with narrowing of the lumen by (a) swelling of the endothelial cell lining, (b) proliferation of smooth muscle cells (SMC) with vacuolization and swelling of the cytoplasm, and (c) with or without thrombi (7-9).

Primary or idiopathic erythermalgia is rare and arises at young age as a bilateral symmetric burning and redness of mainly the lower extremities in the absence of detectable disease (1-3). The diagnosis is made only according to a list of clinical criteria. Its pathogenesis remains elusive, and symptoms persist throughout life and are refractory to any treatment method. Secondary erythermalgia usually occurs at adult age in association with various underlying disorders (1,10-14).

Diagnostic differentiation between primary erythermalgia and erythromelalgia is very important since treatment and, consequently, prognosis differ. Histopathological examination of lesional skin may contribute to recognition of the separate types. Therefore, we performed a histopathological study to seek the underlying cutaneous pathology of primary erythermalgia.

PATIENTS AND METHODS

The study group consisted of three patients with primary erythermalgia. The diagnosis of primary erythermalgia was made according to clinical crite-

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TABLE 1. *Clinical characteristics of three patients with primary erythralgia*

Case/sex/ current age/ age at onset (yr)	Grade	Location	Treatment	Outcome
1/F/15 ^a /9	Severe	Feet/lower legs	Symptomatic	Poor
3/F/31/12	Severe	Feet/lower legs	Symptomatic	Poor
2/F/53/0	Severe	Feet/lower legs	Symptomatic	Poor

^a Died at age 15.

ria as described previously (2). Primary erythralgia is characterized by (a) attacks of bilateral or symmetric burning pain in the hands or feet; (b) attacks initiated or aggravated by standing, exercise, or exposure to heat; (c) relief obtained by elevation of the extremities and exposure to cold; (d) flushing and congestion of the affected parts with increased local heat during attacks; (e) unknown pathogenesis with no treatment available; (f) onset at early age (children and adolescents) and persistence throughout life; (g) relative sparing of the toes and absence of acrocyanotic ischemia and peripheral gangrene; and (h) an autosomal dominant hereditary trait in familial cases.

The pertinent clinical data are shown in Table 1. For histopathological studies, deep punch skin biopsy samples 0.3–0.6 cm in diameter were obtained from lesional skin on the dorsum of the feet. Subsequently, biopsies were fixed in 40% formaldehyde, dehydrated in alcohol, and embedded in Paraplast. Sections 2–4 μ m thick were stained with hematoxylin azophloxine and with the van Gieson stain for light microscopy study. The results of histopathological examination are summarized in Table 2.

RESULTS

Clinical Cases of Primary Erythralgia

Case 1

In 1980, a 9-year-old girl developed painful erythema of both legs below the knee and of both feet,

associated with marked intolerance to heat. Physical exercise worsened the pain. With time, the sensation of burning increased gradually, with occasional paroxysmal pain. The patient attempted to reduce the pain by walking barefoot, by using a ventilator, and later by sitting with the legs in cold water. The pain markedly disturbed her sleeping pattern. Her father and younger brother have or had similar but far less intense symptoms. Since 1983, she had been frequently admitted to the University Hospital in Leuven. At clinical examination, the zones of erythema were consistently described as feeling very warm. The skin of the feet was fissured, and sometimes infected bullae were present, probably as a consequence of prolonged exposure to cold water. The backs of both hands also were erythematous but did not cause complaints. An extensive hematological and immunological investigation on several occasions was negative. Urinary catecholamine level and blood pressure (BP) were intermittently increased, and attributed to stress because extensive investigation, including isotope studies, failed to show a pheochromocytoma. Thermography confirmed the hyperthermia of both feet. Doppler registration of the ankle pulses showed low peripheral resistance, with increased diastolic blood flow. Dermatological treatment improved the skin lesions but not the pain. Between 1983 and 1986, she was treated with aspirin, cinnarizine, ketanserine, antihistaminics, the 5-lipoxygenase inhibitor nafazatrom, corticosteroids, nifedipine, prazosine, nitroprusside, percutaneous regional nerve stimulation, and psychotherapy. She even consulted an acupuncturist. None of these approaches had more than a transient effect. The diagnosis of primary erythralgia was made. In view of the excruciating pain and the lack of any therapeutic relief, the patient became more and more depressed and committed suicide in 1986.

Case 2

From birth, a 53-year-old woman had had persistent, bilateral, warm, and undulating burning pain

TABLE 2. *Cutaneous pathology in three cases of primary erythralgia*

Patient	Epidermis	Histology					Subcutis
		Dermis					
		Perivascular mononuclear cells	Endothelial swelling	Perivascular edema	Thickening of basal membrane of capillaries	Occlusive thrombi	
1	Hyperkeratosis, hyperplasia	Minimal	Moderate	Mild	Moderate to severe homogeneous	Absent	Normal
2	Normal	Moderate/severe	Moderate	Moderate	Moderate to severe lamellar	Absent	Normal
3	Hyperkeratosis	Minimal	Moderate	Marked	Severe lamellar	Absent	Normal



FIG. 1. Painful, burning, and red discolored extremities in a patient with primary erythermalgia.

of her feet, ankles, and the lower parts of her legs. Her hands caused no complaints. She could not tolerate any heat and declined wearing socks and/or shoes because this aggravated the burning distress. She always walked barefoot, even in winter. Nevertheless, she avoided walking, for this and any kind of exercise worsened the discomfort. The burning pain usually awakened her at night, and she sought relief by soaking her feet in ice-cold water. Physical examination disclosed red purplish symmetrical erythema and pitting edema on both feet, ankles, and the lower part of her legs (Fig. 1). Extensive laboratory investigations showed no abnormality; in particular, platelet counts were always within normal limits. The complaints increased with time, and various drugs, including β -blockers, non-

steroidal antiinflammatory drugs (NSAIDs), and aspirin had no effect.

Case 3

Since adolescence, a 34-year-old woman had had slowly progressive burning erythema of the feet and lower legs. Warmth and physical exercise increased the sensation to burning pain and caused intensification of red purplish discoloration and swelling of the feet and lower legs. She walked barefoot even in winter. Multiple laboratory investigations showed no abnormality, and platelet counts were always within normal values. Various drugs, including aspirin, did not alleviate the discomfort. Of her three children, one daughter has similar but much less intense symptoms.

HISTOPATHOLOGICAL FINDINGS

Histopathological findings of skin punch biopsies from affected areas are shown in Table 2. The results from examination of biopsy specimens from all three patients with primary erythermalgia were comparable. Two (cases 1 and 3) had epidermal hyperkeratosis and some mild hyperplasia (Fig. 2). In all cases, the capillary blood vessels showed moderate to severe thickening of the wall (Fig. 2). It had a laminar appearance in two patients (cases 2 and 3) and a homogeneous structure in one (case 1). The endothelial lining of the vessel walls could be moderately swollen, with protrusion of the endothelial cells into the lumen. The striking histopathological appearance in one patient (case 3) was media proliferation of the arterioles in the absence of obvious vascular or inflammatory disease (Fig. 3). These changes were not due to other processes such as

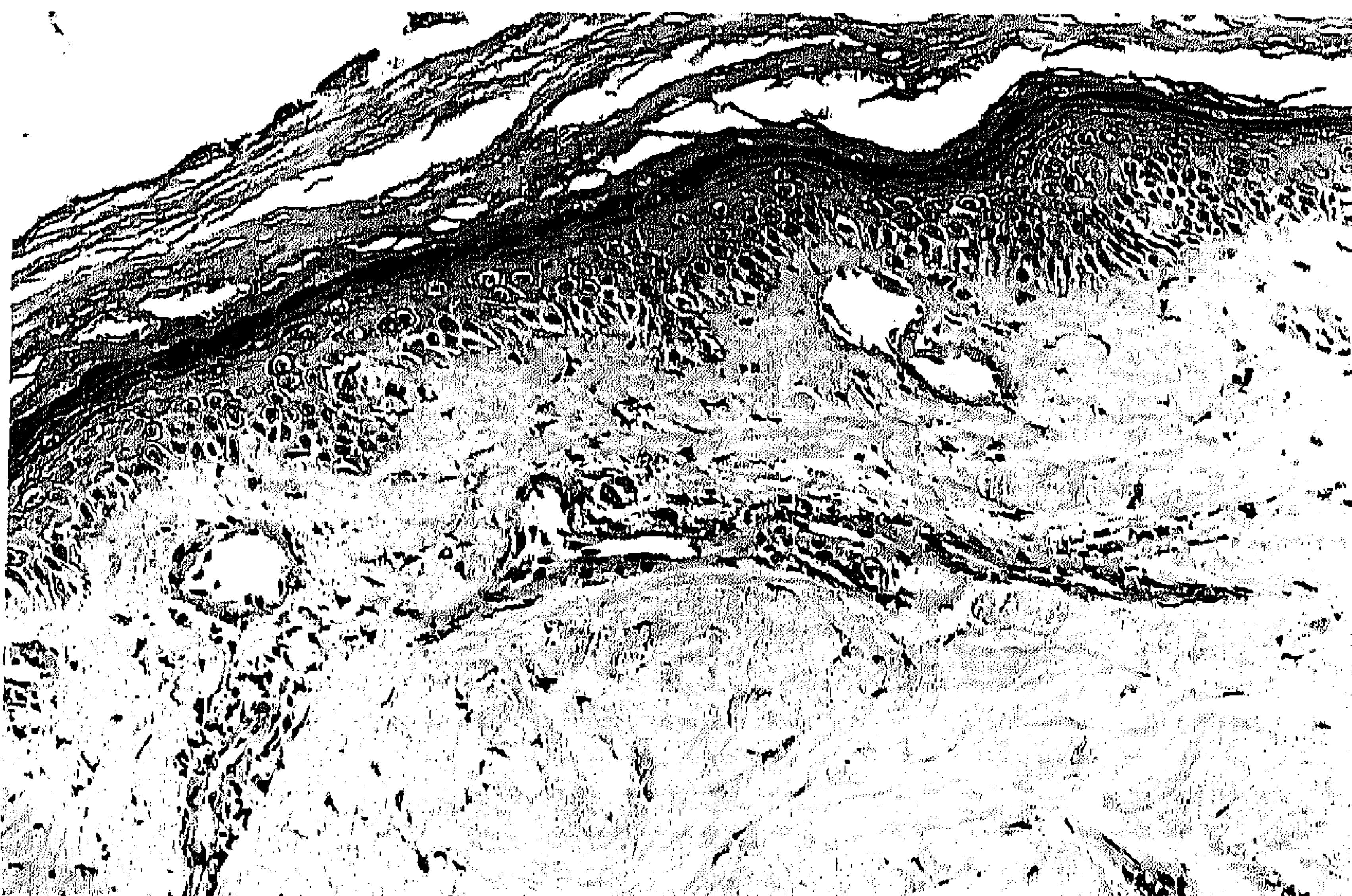
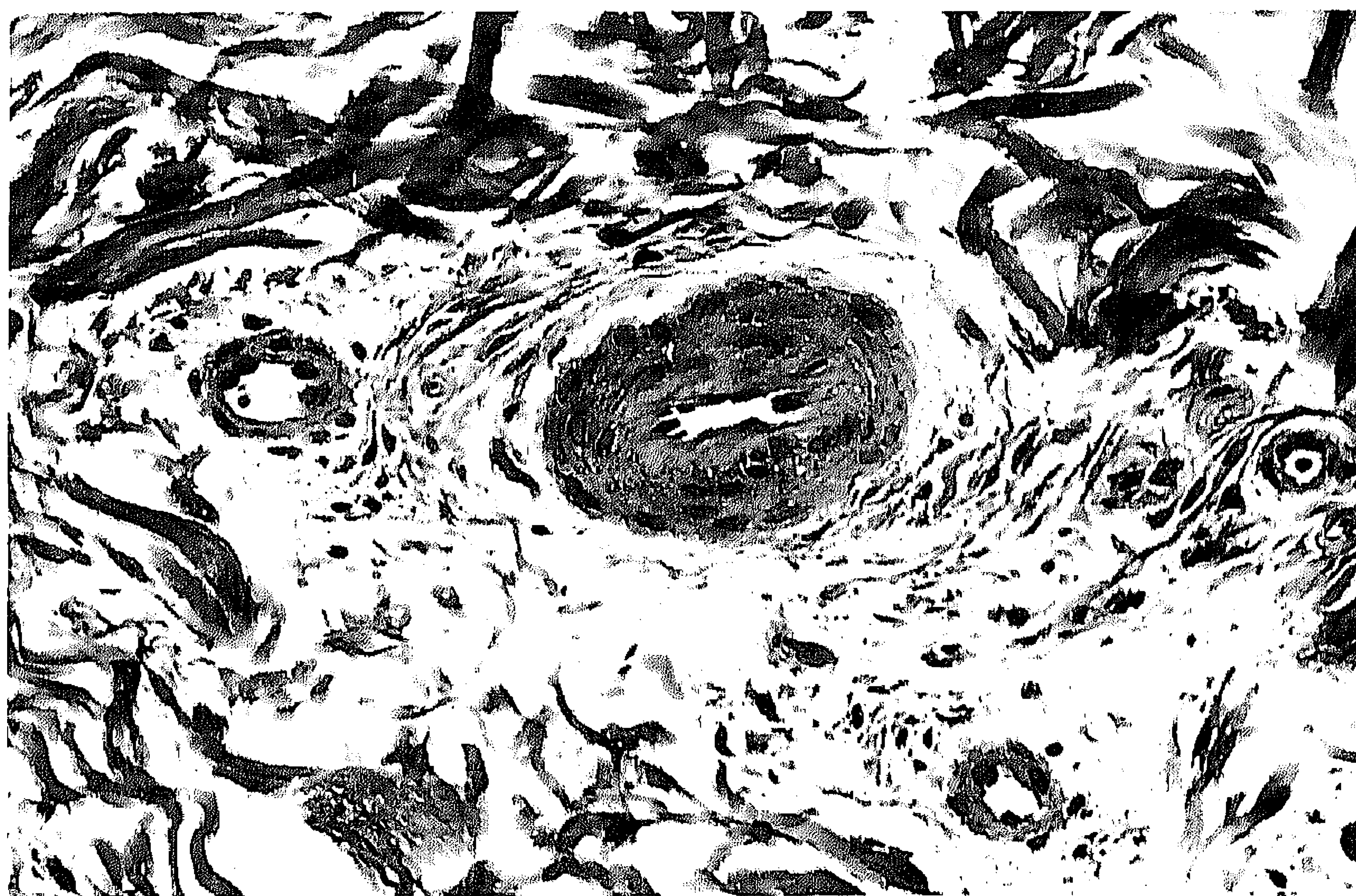


FIG. 2. Capillary blood vessels of the upper dermis, showing slight perivascular fibroplasia as well as endothelial swelling.

FIG. 3. Blood vessel in the upper dermis with severe media thickening. Slight perivascular edema and inflammatory infiltrate are also apparent.



stasis because there were no hemosiderin-laden macrophages, as indicated by a negative finding on staining for iron. All biopsy specimens were characterized by minimal to moderate perivascular inflammatory infiltration, composed solely of mononuclear cells (Fig. 4). Mild to marked perivascular edema was a feature of all biopsy specimens from patients with primary erythralgia. The elastic fibers in all skin layers had a normal appearance (van Gieson stain). The subcutis was normal in all biopsy specimens. Fibromuscular intimal proliferation and occlusive thrombi in the arterioles, typical of erythromelalgia, were absent in all specimens of primary erythralgia (7).

DISCUSSION

We studied the histopathological features of skin punch biopsies from three patients with primary

erythralgia. Primary erythralgia is a rare, incurable disorder of unknown etiology. The slight perivascular mononuclear infiltration apparently represents a response to an as yet unknown pathophysiological process. The poor prospects and the continuous agony of primary erythralgia may cause severe depression and even suicide, as in our case 1. The origin of the syndrome is not understood, but examination of biopsy specimens of affected skin may provide a clue to its pathogenesis. The histopathological findings from biopsy specimens in our cases with primary erythralgia show a clear but slight perivascular mononuclear inflammatory infiltrate. Moreover, the basal membrane of the capillaries is thickened with a lamellar structure and the endothelial cells are swollen. In addition, there is abundant perivascular edema, which may cause the dermal vessels to have a manchette-like appearance. The histopathology of primary

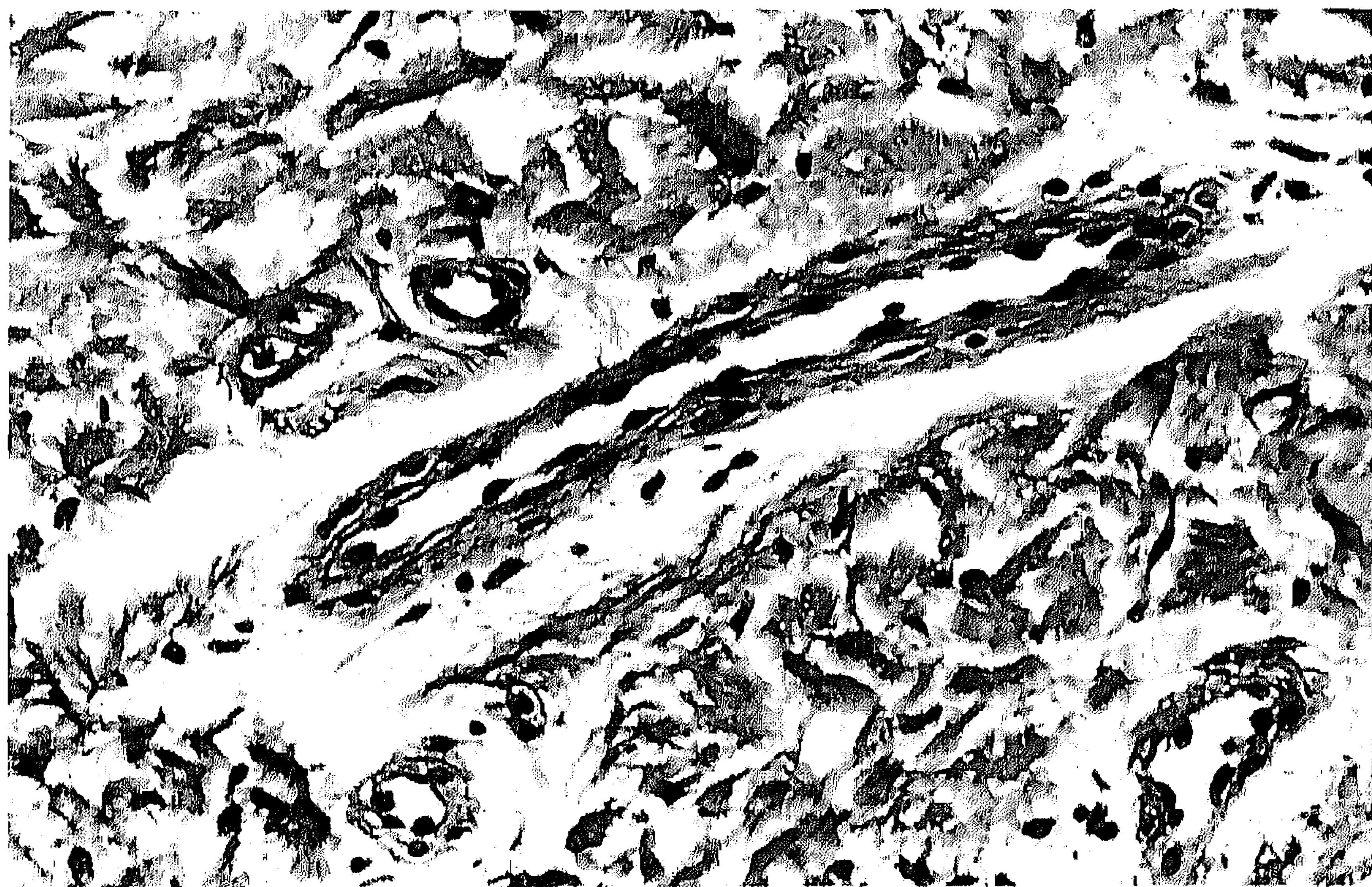


FIG. 4. Capillary blood vessels in the lower dermis. The vessel wall has a lamellar appearance, with perivascular edema and thickening.

erythermalgia was reported occasionally in four cases (15–18). Sections from two cases showed normal dermal vascular structures lined by flat endothelial cells (15,16). Biopsy specimens from a third case demonstrated dilated and proliferating capillaries and increased dermal collagen content (17). Skin punch biopsy specimen from the fourth patient showed a swollen endothelium of the dermal vessels and a slight lymphocytic perivascular infiltrate (18). In contrast, the pathological changes in erythromelalgia, which result from platelet-mediated processes in the arteriolar circulation, are characterized by (a) endothelial cell swelling, (b) proliferation of SMC, and (c) deposition of intracellular platelet plugs (7). In long-standing cases of erythromelalgia, fibromuscular intimal proliferation develops; ultimately, the tissues become completely fibrosed. Administered in an early stage, aspirin reverses the vascular changes in erythromelalgia but does not alleviate symptoms in primary erythermalgia (19).

Our findings in primary erythermalgia do not provide a clue to its pathogenesis but are essentially different from the specific pathological findings in erythromelalgia and erythermalgia secondary to cutaneous vasculitis, in association with systemic lupus erythematosus in particular (10,11,13). Primary erythermalgia is histopathologically featured by slight but clear moderate perivascular mononuclear cell invasion, endothelial cell swelling, perivascular edema, and slight to moderate thickening of the basal membrane of the capillaries. Histopathological examination of affected skin lesions in patients with red, warm, and painful burning extremities is a valuable tool in the diagnostic process for the differential diagnosis between erythromelalgia and erythermalgia.

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