

Erythromelalgia caused by platelet-mediated arteriolar inflammation and thrombosis in thrombocythemi

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Erythromelalgia was the presenting symptom in 26 of 40 patients with thrombocythemia in its primary form or when associated with polycythemia vera. The localized painful burning, redness and warm congestion in the extremities could be accurately documented with thermography. Skin punch biopsy samples taken from the affected areas showed typical arteriolar inflammation, fibromuscular intima proliferation, and thrombotic occlusions. Erythromelalgia often progressed to ischemic acrocyanosis or necrosis in toes or fingers. Complete relief of pain and restoration of microvascular circulation disturbances was obtained with the cyclo-oxygenase inhibitors aspirin and indomethacin, but not with sodiumsalicylate or the platelet inhibitors dipyridamole, sulfinpyrazone, ticlopidine, and dazoxiben. The erythromelalgia was alleviated during busulfan-induced remissions of thrombocythemia and its recurrence coincided with relapsing thrombocythemia. These observations suggest a causal relationship between erythromelalgia and thrombocythemia, in which platelet mediated inflammatory and occlusive arteriolar changes play a part in the etiology of erythromelalgia.

Mitchell (1) first reported a syndrome of redness and burning pain in the extremities, which he labeled erythromelalgia. Brown (2) postulated five basic criteria for erythromelalgia: the attacks consist of burning pain in feet or hands; the pain is initiated or aggravated by standing, exercise, or exposure to heat; the pain is relieved by elevation or cooling of the affected limb; the painful areas are red, congested, and warm; and the condition is refractory to treatment. The term erythromelalgia has been used by Smith and Allen (3) to emphasize inflammation and warmth. The relief of pain for several days after a single low dose of aspirin is specific for erythromelalgia and can be used as a diagnostic criterion (3-5). Erythromelalgia has been divided into a primary form without underlying disease, and a secondary form in connection with various diseases, polycythemia vera in particular (3, 4). Evidence is accumulating that erythromelalgia is especially related to chronic myeloproliferative disorders; it may be a clue to the diagnosis of polycythemia vera (6, 7) or primary thrombocythemia (8-11).

In this study involving 26 patients we show that erythromelalgia is a separate microvascular disorder that appears to be an expression of underlying thrombocythemia in its primary form or associated with polycythemia vera. The effect of different platelet inhibitors and analgesic agents on the erythromelalgic symptoms was studied in correlation with thermography of the affected areas and the degree of malondialdehyde synthesis in blood platelets.

Methods

Hematologic and biochemical data were routinely obtained. Erythrocyte mass was measured with the ⁵¹Cr sodium chromate-labeled autologous erythrocytes and plasma volume with ¹³¹I human serum albumin. The leukocyte alkaline phosphatase score was determined with the cytochemical technique of Kaplow (12). Bone marrow biopsies were done with a Jamshidi needle. Sections were stained with hematoxylin azophyloxine and with the Gordon and Sweet stain for reticulin.

Thermography was done with a Bofors Mark II camera (Karls Koga, Sweden) that registers the skin surface temperature indirectly (13). Temperature differences were recorded on a color scale gauged to a fixed reference temperature. The spleen size was expressed in centimeters of its longitudinal diameter on the basis of scintigraphic visualization with ^{99m}Tc sodium pertechnetate. Malondialdehyde production in platelets was measured according to the methods of Smith and associates (14).

For histopathologic studies of erythromelalgic areas, deep punch skin biopsy samples of 0.3 to 0.6 cm in diameter or wedge excisions were fixed in 40% formaldehyde, dehydrated in alcohol, and embedded in paraplast. Sections of 2 to 4 μm thickness were stained with hematoxylin azophyloxine.

All patients cooperated voluntarily in the study after being fully informed by the responsible physician.

Results

CLINICAL SYMPTOMS

Twenty-six of forty patients with thrombocythemia presented erythromelalgic symptoms (Table 1): 13 with primary thrombocythemia and 13 with polycythemia vera. Peripheral blood counts showed a persistent thrombocytosis. Diseases predisposing to vascular occlusion such as obliterative arteriosclerosis, diabetes, infections, malignancy, or other systemic diseases were not found. Polycythemia vera was diagnosed according to the criteria proposed by the polycythemia vera study group (15). The ages of the patients with primary thrombocythemia and those with polycythemia vera ranged from 33 to 72 years (mean, 48) and from 49 to 75 years (mean, 62), respectively.

Erythromelalgic areas, when bilateral, were usually asymmetric. The sole of the forefoot, or one or more toes were affected in 20 patients, and the tips of the fingers in 8.

Erythromelalgia was initially felt as an itching and prickling sensation, often like pins and needles, which in time progressed to scorching, burning pain and acrocyanosis, provoked particularly by exercise or warmth. In several cases the discomfort was aggravated to such a degree that the patient had to sit with his feet elevated; in this position the acrocyanosis and pain usually subsided. Three patients developed necrosis of a nailfold, four of a toe tip, and two of a whole distal toe phalanx.

Table 1. Erythromelalgia and Ischemic Circulation Disturbances in Patients with Primary Thrombocythemia or Polycythemia Vera

Patient	Sex/Age (yrs)	Platelet Count X 10 ⁹ /L	Erythromelalgia*			Peripheral Gangrene*	Interval*** Months
			Feet	Fingers	Skin		
Primary thrombocythemia							
1	F/60	792	++	-	+	+	45
2	M/54	887	++	-	-	+	154
3	F/42	911	-	+	+	-	60
4**	M/47	614	+	-	-	+	12
5	M/46	930	+	-	-	+	64
6	M/33	742	+	-	-	-	20
7**	M/45	576	++	-	+	-	60
8**	M/39	875	++	++	+	-	30
9	M/51	690	++	-	-	+	20
10	M/40	1440	+	-	-	+	30
11	F/72	1445	+	-	-	-	30
12**	M/40	1190	++	-	+	-	29
13**	M/72	1432	++	-	-	-	11
Polycythemia vera							
14	M/67	1932	++	-	-	-	24
15	F/64	1800	-	+	+	-	3
16	M/54	942	++	-	-	-	0
17	M/53	636	+	-	-	+	36
18	F/64	1065	++	-	-	-	48
19	F/47	728	-	++	-	-	1
20	M/66	1035	++	-	-	-	18
21	M/71	1320	+	-	-	-	2
22**	M/55	1300	+	-	-	+	24
23	F/57	1085	-	+	-	-	4
24**	F/59	708	-	++	+	-	3
25**	F/74	950	+	+	-	-	24
26**	M/71	609	-	+	-	-	6

* + = unilateral; ++ = bilateral; - = absent
 *** Time between the onset of erythromelalgia and diagnosis of thrombocythemia.
 ** Thermography done for this patient.

The lapse between the first symptoms of painful acre and the diagnosis of thrombocythemic erythromelalgia, for which medication or surgical intervention had usually been unsuccessfully tried, ranged from a few months to several years, with a median of 18 months when only erythromelalgia was present, and 33 months when peripheral necrosis had occurred. Thrombophlebitis had been diagnosed in four of seven patients with painful and indurated skin areas of the upper legs; arteriosclerosis or vasculitis was diagnosed in the others.

LABORATORY FINDINGS

The erythrocyte sedimentation rate was low (1 to 4 mm/h) in all patients. Hemoglobin

values were normal in patients with primary thrombocythemia but elevated in patients with polycythemia vera. The leukocyte counts were normal to slightly elevated in both groups. The leukocyte alkaline phosphatase score was elevated in 11 of the patients with primary thrombocythemia, and in all of the patients with polycythemia. Absolute basophil counts were low in all patients. The platelet counts were always above $500 \times 10^9/L$, being more than $1000 \times 10^9/L$ in 4 patients with primary thrombocythemia and seven with polycythemia.

In all patients bone marrow smears and biopsy samples showed clustering and an increase of mature megakaryocytes. An increase of reticulin fibers together with high bone marrow cellularity was found in seven patients with primary thrombocythemia and all patients with polycythemia.

The spleen size in patients with primary thrombocythemia was normal (less than 12 cm longitudinal diameter) in seven and enlarged (12.5 to 16 cm longitudinal diameter) in four. The spleen was not found by scintigraph in one patient, and had been removed in another with primary thrombocythemia. In the group with polycythemia the spleen was normal in two patients and enlarged (13 to 18 cm longitudinal diameter) in ten; one patient had had a splenectomy.

Thermography was done in nine patients, and the erythromelalgic areas could be seen in all. The skin surface temperature always exceeded $31^\circ C$, and sometimes reached $36^\circ C$. Differences of up to $9^\circ C$ with the corresponding contralateral skin area were common. At the time of positive thermography the posterior tibial and dorsal foot arteries were found to pulsate normally by palpation. A representative isothermogram is shown in Figure 1.

Skin biopsy samples from affected areas of classic erythromelalgia that had recently relapsed after discontinuation of aspirin were examined for histopathologic characteristics. The skin sections show arteriolar lesions without involvement of venules, capillaries, or nerves (Figure 2). The endothelial cells are swollen. The inner layer of the vessel wall is thickened by proliferation of cells with vacuolization and swelling of the cytoplasm and deposition of intercellular material. Details are reported elsewhere (16). Narrowing of the arteriolar lumen appears to occur by proliferation of smooth muscle cells, splitting the internal elastic membrane, and giving rise to the appearance of fibromuscular intima proliferation. Arterioles were often occluded by thrombi of different age and had become completely fibrosed when peripheral necrosis had occurred.

TREATMENT

After a single 500-mg dose of aspirin the pain in the extremities was alleviated within a few hours, while the inflammatory signs vanished in about 1 to 2 days (Figure 1). As shown in Figure 3, relief of pain from one oral dose of aspirin, 500 mg, lasted 4 days, but from one oral dose of indomethacin, 25 mg, only 24 hours. This analgesic effect is in accordance with the length of inhibition of platelet malondialdehyde production by these drugs. Sulfinpyrazone, 800 mg, dipyridamole, 400 mg, or ticlopidine, 1000 mg, daily for 5 days, did not alleviate the symptoms, but also had no effect on platelet malondialdehyde production (data not shown).

Dazoxiben, a thromboxane synthetase inhibitor, 1600 mg/d, completely inhibited platelet malondialdehyde production but appeared to be ineffective on erythromelalgia. The analgesic agents sodium salicylate, glafenin, acetaminophen, and pentazocine and the serotonin antagonist methysergide had no appreciable effect on the erythromelalgic pain. Anticoagulation with coumarin, which had been given to four patients developing tissue necrosis (Patients 1, 2, and 9 with primary thrombocythemia and Patient 17 with polycythemia; Table 1) had no therapeutic effect. However, subsequent treatment with aspirin, 500 mg/d, not only relieved the pain but also markedly improved the circulation and healing process.

The results of treatment are shown in Figure 4. Remission of thrombocythemia (platelet counts of less than $350 \times 10^9/L$) induced by busulfan lasted from 2 to more than 9 years and were associated with the disappearance of erythromelalgia. Patients 4, 7, 12, and 13 with primary thrombocythemia and Patients 16, 19, 20, and 26 with polycythemia received long-term aspirin therapy, which gave complete symptomatic relief and circulatory improvement for the duration of administration. Bloodletting in polycythemia vera did not improve erythromelalgia. Erythromelalgia recurred in 8 of 12 patients when thrombocythemia relapsed at platelet counts of 400 to $550 \times 10^9/L$. Patients 21 and 22 with polycythemia died as a result of unrelated cardiac failure and lung carcinoma, respectively.

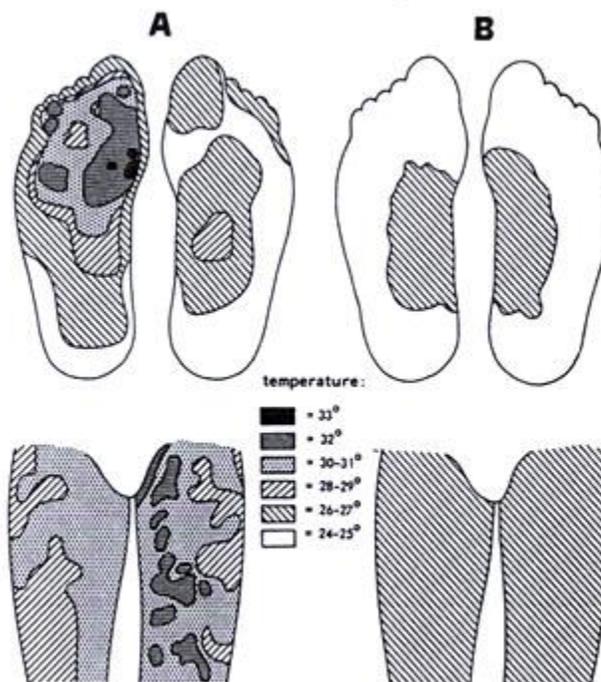


Figure 1. Isothermograms of the soles of the feet and the skin of the upper legs in a patient with thrombocythemia and erythromelalgia before (A) and 2 days after (B) treatment with aspirin.

Discussion

The erythromelalgic symptoms, which occurred in two thirds of our patients with thrombocythemia in its primary form or when associated with polycythemia vera, are identical to those reported for primary erythromelalgia (1, 3). Polycythemia in itself was not pathogenic, because blood-letting did not improve the erythromelalgic symptoms. Reduction of the platelet counts to a normal level with busulfan, however, abolished erythromelalgia both in primary and in polycythemic thrombocythemia. We did not see erythromelalgia in 18 cases of reactive thrombocytosis or chronic myelocytic leukemia with an excess of platelets, indicating that not only the platelet number but also a qualitative abnormality of the platelets induces erythromelalgia.

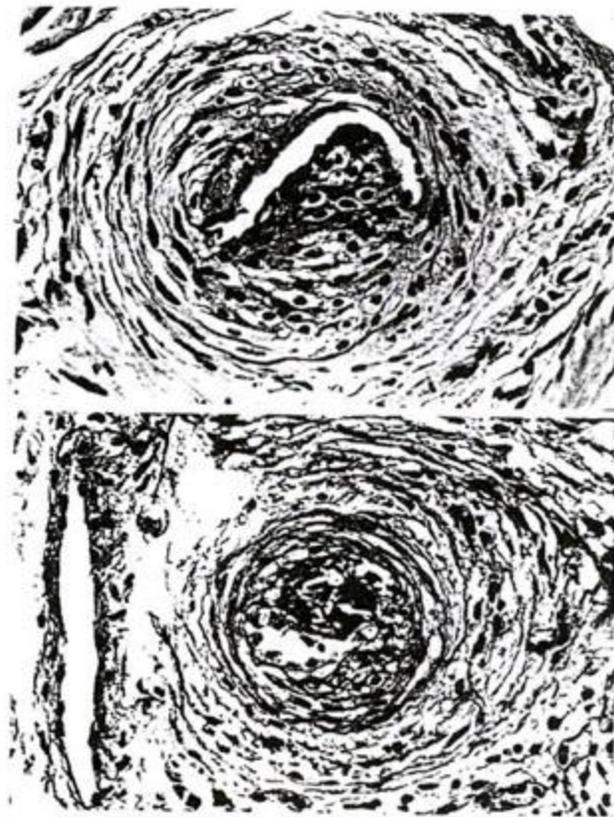


Figure 2 Top. Arteriole with pronounced cell proliferation of the inner layer of the media and degenerative cytoplasmic swelling. Figure 2 Bottom. Thrombotic occlusions of an arteriole with proliferative vessel wall changes. (Hematoxylin and azophloxine; original magnification, $\times 380$.)

In our experience the typical intermittent prickling and pins and needles sensations in the extremities (3) usually precede, or interchange with, episodes of the classic burning and disabling distress of erythromelalgia. The intensity of the pain correlates well with the degree of skin temperature. Burning pain was present when the thermographic surface temperature exceeded 31°C , which is in agreement with the direct measurements of Brown (2) and Smith and Allen (3). We could also confirm the observation that erythromelalgia disappears for 2 to 4 days after a single dose of aspirin (3). This period is similar to the duration of inhibition of aggregation and prostaglandin synthesis of exposed platelets, due to irreversible inactivation of cyclo-oxygenase by aspirin (17,18). Indomethacin, which reversibly inhibits platelet cyclo-oxygenase (19, 20), improves erythromelalgia for less than 24 hours; sodium salicylate, sulfinpyrazone, dipyridamole, and ticlopidine have no effect at all on erythromelalgia, but have no cyclo-oxygenase inhibiting activity (21-23). Thus, active platelet prostaglandin metabolism is necessary for erythromelalgia to develop.

The statement by Brown (2) that the syndrome of erythromelalgia is based on

vasodilatation without microvascular occlusions is in conflict with the original case descriptions (I, 3) and also with our experience. Pain with red congestion may develop into local coldness with cyanosis and even necrosis of the tip of a toe or finger. In contrast to arteriosclerotic circulatory obstruction the peripheral arterial pulsations usually remain normal. Skin biopsy samples from areas of classic erythromelalgia consistently show various degrees of inflammation, smooth muscle cell proliferation, and thrombotic occlusions confined to the arterioles (16). These histologic lesions clearly show the pathophysiologic spectrum of erythromelalgic symptoms and signs. In other studies we obtained evidence that there is increased consumption of platelets during active erythromelalgia, which is normalized by aspirin but not by coumarin (24).

All of the above findings suggest that the symptoms of erythromelalgia are the result of platelet activation and aggregation *in vivo*, which preferably takes place in the arterioles. It is possible that the high shear rate of the blood flow in arterioles as compared to that in arteries contributes to this localization (25). Prostaglandins and thromboxanes, derived from activated platelets, may account for the inflammatory symptoms, and the platelet derived growth factor, released by activated platelets (26), may be responsible for the arteriolar intimal thickening due to proliferation of smooth muscle cells (16). Surprisingly, inhibition of thromboxane synthetase by dazoxiben in three patients did not relieve erythromelalgia and did not correct the increased platelet consumption. Therefore it may be that not thromboxane A₂, but its direct precursors, the endoperoxides or Prostaglandins E₂ in particular, are responsible for the pain and inflammation (27, 28) associated with erythromelalgia.

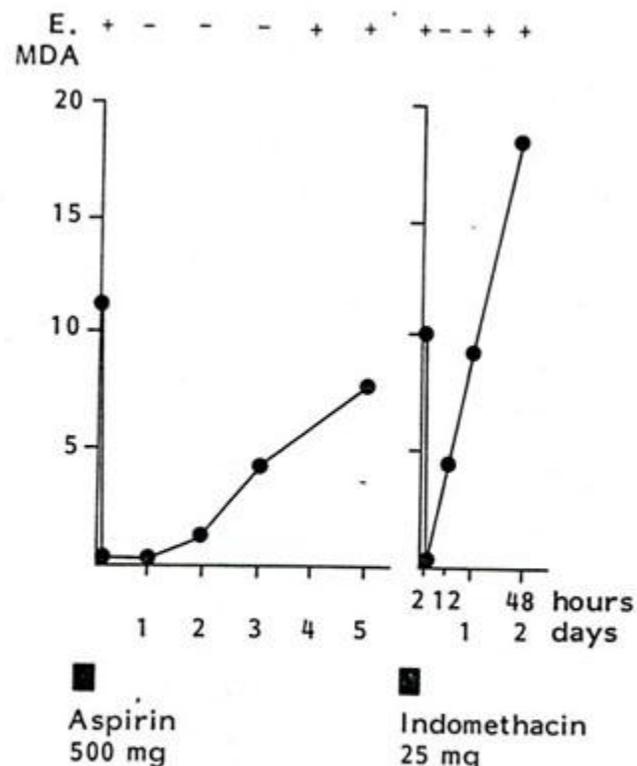


Figure 3. The effect of aspirin, 500 mg (left), and indomethacin, 25 mg (right), on erythromelalgic pain (E) and arachidonic acid-stimulated platelet malondialdehyde (MDA) synthesis (nmol/10⁹ platelets) in a patient with thrombocythemia. + = present; - = absent.

Erythromelalgia is frequently not recognized, probably because of unfamiliarity with its typical clinical appearance. Moreover, several cases that have no or only slight resemblance to this condition have been reported as erythromelalgia (29-32). The

differentiation from inflammatory and circulatory disturbances on the basis of gout, arteriosclerosis, diabetes mellitus, systemic lupus erythematosus, rheumatoid arthritis, eczema, cryoglobulinemia, immune complex, and other vasculitic disorders may sometimes be difficult. The long-lasting relief given by aspirin, lacking in other diseases, is the most diagnostic test for erythromelalgia. Peripheral platelet counts may be only moderately elevated; however they often increase considerably during periods of aspirin intake. Moreover, other hematologic findings such as increased and clustered megakaryocytes in the bone marrow, leukocytosis, elevated leukocyte alkaline phosphatase, and a high hematocrit may sustain the suspicion of a myeloproliferative disorder. We hope that the reported coincidence of painful toes or fingers, acral redness, cyanosis, or gangrene, with primary or polycythemic thrombocythemia (7, 9, 33-40), may become a more defined clinical entity, when framed in the clinical, pathophysiologic, and histologic picture of erythromelalgia.

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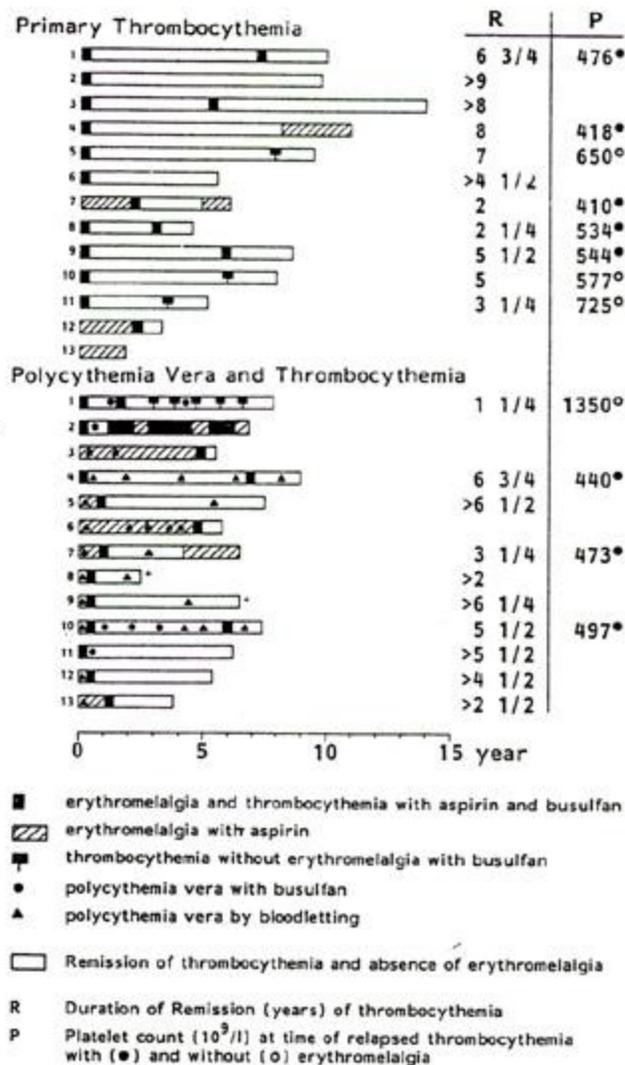


Figure 4. Results of treatment in 13 patients with primary thrombocythemia and 13 patients with polycythemia vera and thrombocythemia.

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