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REVIEW

ERYTHROMELALGIA AND ERYTHERMALGIA:
DIAGNOSTIC DIFFERENTIATION

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The current study outlines the historic development and crystallization of nomenclature of a syndrome of red, warm, swollen, and painful extremities. This syndrome can be divided into three types: erythromelalgia, primary erythermalgia, and secondary erythermalgia. We have recognized that a subset of patients who experienced clinical relief with aspirin had elevated platelet counts either associated with primary thrombocythemia or thrombocythemia associated with another chronic myeloproliferative disorder, polycythemia vera in particular. This form is defined as a distinct clinical entity and depicted as erythromelalgia. On the basis of 10 characteristics, erythromelalgia is set apart from other forms of red, warm, and painful extremities in the absence of thrombocythemia, which we labeled erythermalgia. Erythermalgia occurs in two different forms. Primary erythermalgia appears to arise at a young age as a bilateral symmetric burning and redness of mainly the lower extremities in the absence of detectable disease. Secondary erythermalgia is typified by red, warm, swollen, and painful extremities in the absence of thrombocythemia. This entity is linked to other (vascular) illnesses or the use of drugs. Secondary erythermalgia usually responds to treatment of the underlying disease or stoppage of the incriminated drug.

HISTORIC OUTSET OF TAXONOMY

Mitchell, as a physician to the orthopedic hospital and infirmary for nervous diseases of Philadelphia, reasoned that it is often a good and practiced mode of teaching to present a collection of cases united in appearance by some common and prominent feature. This can then be traced back to its various causes, illustrating the diverse

ways the disease can present originally.¹ In his authentic clinical lecture on certain painful affections of the feet, Mitchell reported on painful muscle spasms in the feet of two patients that were relieved after tendectomy of the involved muscles, and on painful violent contractions of the right gastrocnemius muscle in an 11-year-old child that were entirely cured after a long illness with remittent fever. In his second lecture on certain painful affections of the feet, Mitchell pointed to another form of foot pain.² Here, he first reported on bilateral burning pain and purple red congestion in the feet in four adults, aged 21–40 years. In all, the burning distress was elicited by exercise and warmth. Relief was obtained by both cooling of the affected lower extremities and rest. Because these two contributions on painful affections of the feet attracted little attention, he found himself called upon by a larger and more fertile knowledge to review the subject in an original paper entitled, "On a rare vasomotor neurosis of the extremities and on the maladies with which it may be confounded."³ In a footnote on the title page of this paper he stated that the foot and hand disorder might be conveniently labeled erythromelalgia, deriving it from the Greek words: erythros = red, melos = extremity, and algos = pain. Based on his observations in 16 cases he noted some common appearances. The complaints begin with pain in the foot or feet; usually it starts in the ball of the foot or of a great toe and may extend to the dorsum and even the leg. More often, the pain is felt in a limited region of one or both soles and does not extend beyond these areas.

The pain is of a burning character and often so characteristic as to be clinically distinctive. In milder cases the burning distress may come and go, while in severe cases the throbbing, aching, and burning pain reaches the extremes of torture. The pain, in all, is relieved or arrested by cold. Symptoms are brought on and made worse by exposure to warmth, by standing, walking, and exertion. Patients sleep with uncovered feet and prefer to walk barefooted. The striking peculiarity of the disorder is the flushing of the involved extremity. The area of the greatest pain in the sole or hand is marked by a dull, dusky, mottled redness until the extremity gets a dark purplish tint. Finally, the patients are rarely amenable to treatment. In 1899, Mitchell and Spiller noted that the above described type of erythromelalgia typically may be seen in younger adults

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and that there are variations in older persons.⁴ Osler, in a later paper, mentioned that the red painful extremities in cases of polycythemia vera may simulate erythromelalgia of Weir Mitchell.⁵ Oppenheimer was the first to recognize that erythromelalgia may precede the hypervolemic symptoms of polycythemia vera.⁶

As the pathologic basis of erythromelalgia had not been established, the original concept as outlined by Mitchel has been lost. The subsequent literature on erythromelalgia is very confusing.⁷⁻¹² Many different forms of vascular and neurologic disturbances have been erroneously classified as examples of erythromelalgia. Redness and pain of the feet are present in erythromelalgia as well as in many other conditions: gout, thromboangiitis obliterans, localized arteriosclerotic lesions in the feet, cellulitis involving the lower legs, feet, or hands, and even in certain cases of Raynaud's disease, to give some examples.

In 1932, Brown separated the group of typical cases with the primary variant from those cases in which there was burning pain in the hands and feet secondary to diseases.¹³ The hot, burning disturbances of acral portions as a frequent precursor or an early single presenting symptom of polycythemia vera were mentioned as the most prominent and typical variant of secondary erythromelalgia.^{14,15} As the term "erythromelalgia" was thought not to be adequate because it did not denote the importance of heat, Smith and Allen in 1938 proposed to substitute it for another descriptive term, namely erythermalgia. They further pointed out that the condition should be divided into a primary (idiopathic) and secondary (related to nervous, peripheral vascular, or other diseases) type.¹⁶ Since then, the terms erythromelalgia and erythermalgia are used indiscriminately as synonyms in the primary and secondary forms.¹⁷ In the coming paragraphs we introduce the historic differentiation of this syndrome to erythromelalgia and primary erythermalgia on the basis of recent clinical and laboratory studies.

ERYTHROMELALGIA

Based on elegant clinical, histopathologic, and platelet kinetic studies in a consistent large series of patients, Michiels and his co-workers have elucidated the specific manifestations and pathophysiology of erythromelalgia.¹⁸⁻²⁴ There are 10 typical features of erythromelalgia which are necessary for the diagnosis:

1. Erythromelalgia in its classic manifestation is characterized by red, warm, congested extremities, and painful burning sensations, with preferential involvement of the forefoot, sole, and one or more toes and fingers.¹⁸
2. Warmth intensifies the discomfort and cold provides relief.¹⁸

3. Acroparesthesias (e.g., tingling, pins-and-needles sensations and numbness in toes and fingers) usually precede the disabling burning distress.¹⁸
4. The prompt relief of pain lasting for a few days by a single dose of aspirin is so specific for erythromelalgia that it can be used as a pathognomonic diagnostic criterion.¹⁸
5. If left untreated, erythromelalgia usually progresses to intense burning, throbbing, and aching with peeling of the skin of affected toes or fingers that subsequently become cold or even gangrenous.²¹
6. Erythromelalgia is linked tightly to thrombocythemia in its primary form or is associated with polycythemia vera. Symptoms are caused by platelet-mediated inflammation and thrombosis in the endarterial microvascular circulation. Erythromelalgia in polycythemia vera is not relieved by blood-letting because the thrombocythemia persists.¹⁸
7. The histopathologic features of skin biopsies from affected skin are overshadowed by nonspecific inflammation, by specific fibromuscular proliferation, and thrombotic occlusions of the arterioles in the absence of pre-existent vascular disease.¹⁹
8. Complete relief of erythromelalgia and its ischemic circulatory disturbances is accomplished with continuous low dose aspirin by its irreversible inhibition of platelet cyclooxygenase activity. Reducing the platelet count to normal levels ($350 \times 10^9/L$) abolishes the symptoms.²⁰
9. Evidently, shortened platelet survival in thrombocythemia complicated by erythromelalgia and its correction by curative treatment with aspirin indicate that the symptoms are provoked by intravascular platelet activation and aggregation *in vivo*, which preferably takes place at high shear rate conditions in the arterioles.²²
10. As erythromelalgia does not occur in reactive thrombocytosis, it is postulated that not only a quantitative, but also an unknown qualitative disorder of platelet function in thrombocythemia leads to an increased risk of microvascular thrombotic complications, and not only involving the peripheral, but also the coronary and cerebral circulations.²⁵

The clinical and thermometric manifestations in the five cases of Smith and Allen¹⁶ are characterized by burning distress involving the forefoot or toes, extremities that are entirely dependent on elevation of the skin temperature of the affected parts. In their experiences primary "erythromelalgia" and erythromelalgia secondary to polycythemia vera are essentially the same.

Surprisingly, Smith and Allen noticed that acetylsalicylic acid in amounts as little as 0.65 g produced marked relief of the burning distress that persisted for as long as several days. Although no adequate explanation of this favorable effect was available at that time, Smith and Allen subsequently learned to suspect ery-

thromelalgia, whenever a patient mentioned marked and prolonged relief as a result of using this drug.¹⁶ At least three, if not all five patients from their series with burning, red, congested extremities are consistent with our diagnosis erythromelalgia, since the symptoms in these patients were characteristically relieved by aspirin. Babb and colleagues from the Mayo Clinics reviewed 51 cases of red, warm, swollen, and burning extremities. Thirty cases were recognized as primary and 21 as secondary to other diseases, including polycythemia vera in 9, hypertension in 6, diabetes mellitus in 2, and myeloid metaplasia, venous insufficiency, systemic lupus erythematosus, and rheumatoid arthritis in one case each.¹⁷ Eleven patients with the primary variable and 14 of 18 patients with the secondary variable responded pathognomonically to low dose aspirin, which is the major trait of erythromelalgia.¹⁷ In retrospect, the aspirin-responsive patients from the studies by Smith and Allen¹⁶ and those of Babb and colleagues¹⁷ diagnosed as primary and secondary “erythromelalgia/erythermalgia” can now be labeled as true erythromelalgia. Thus, the aspirin-responsive cases of primary “erythromelalgia” in the old literature have lost their idiopathy. At that time the diagnosis of primary thrombocythemia, as a variant of the chronic myeloproliferative disorders, was unknown. In a subsequent study of 8 patients from the Mayo Clinics, aspirin-responsive “erythermalgia” was a clue to early diagnosis of chronic myeloproliferative disorders, which appeared to be associated with thrombocythemia in at least 7 cases as documented in Table 1 of that report.²⁶

The time-lapse between the onset of symptoms and the diagnosis “myeloproliferative disorder” ranged from 1 to 16 years (mean 6 years). We now label these patients as “erythromelalgia in thrombocythemia” that, in our experience, may precede the onset of polycythemia for several to more than 10 years. At later occasions, painful red or blue toes and fingers or peripheral gangrene in primary thrombocythemia has not been recognized as erythromelalgia despite the characteristic response to aspirin.²⁷⁻²⁹ The occurrence of erythromelalgia in primary thrombocythemia has been occasionally recognized since 1977.³⁰ The etiology and pathophysiology have been completely elusive until we unraveled that all its specific features are causally related to the chronic myeloproliferative disorders, in which platelet-mediated inflammatory and thrombotic processes due to throm-

bocythemia vera occur in the endarterial microvasculature not only of the extremities, but also involving the coronary and cerebral circulations.²³⁻²⁵

PRIMARY ERYTHERMALGIA

On the basis of the description of Mitchell in 1878 and clinical observations in 81 cases in which burning pain in the hands or feet was a prominent or disabling symptom, Brown in 1932 postulated five basic criteria as necessary for the diagnosis of this true primary variant.^{3,13} The characteristics were:

1. Attacks of bilateral or symmetric burning pain occurred in the hands or feet;
2. The attacks were initiated or aggravated by standing, exercise, or exposure to heat;
3. Relief was obtained by elevation and exposure to cold;
4. During the attacks, the affected parts were flushed and congested and exhibited increased local heat; and
5. The pathogenesis is unknown and there is no treatment available.

Following the five postulates of Brown, the rare and incurable variant of red, painful extremities in the absence of any detectable underlying disorder has been recognized by Michiels as a distinct clinical entity and therefore labeled as primary erythermalgia.³¹⁻³⁴ As has become clear from the postulates of Brown, our experiences undoubtedly confirm that the clinical manifestations of primary erythermalgia are in essence completely different from erythromelalgia in thrombocythemia.^{31,34}

In extension to the five postulates of Brown, there are four additional specific features of primary erythermalgia:

6. Primary erythermalgia spontaneously arises in children and adolescents as burning pain and red congestion in the feet, ankles, and lower legs that persists throughout life. In the earlier series of patients diagnosed as “primary erythermalgia” from the Mayo Clinics by Babb et al. only 2 of 30 patients were young (<20 years) at the time of onset of the disease, early onset is nowadays conceived to be essential for primary erythermalgia.¹⁷
7. There is relative sparing of the toes and acrocyanotic ischemia; peripheral gangrene as the result of peripheral vessel obstruction is never seen. Trophic changes, ultimately ulceration, and even necrosis do not result from the disease but are the consequences of excessive cooling.³⁵
8. From various studies the hereditary basis of primary erythermalgia has become clear. In a recent study in one large family with 29 affected members in three generations, an autosomal dominant trait ap-

Table 1. Nosologic Classification of Burning, Painful, Red Congested Extremities according to Drenth and Michiels

<i>Classification</i>	<i>References</i>
Erythromelalgia in thrombocythemia	16,18-25
Primary erythermalgia	13,31-34,37,38
Secondary erythermalgia	31-33,40-44

pears likely.³⁶ The early and spontaneous onset in life and the persistence throughout life further support the congenital nature of the disease.^{37,38}

9. The histologic findings in skin biopsies from erythralgic areas are nonspecific, showing the absence of an underlying disorder and thus do not reveal a clue to its pathophysiology.^{34,39}

SECONDARY ERYTHERMALGIA

As outlined above, thrombocytemic erythromelalgia and primary erythralgia are two completely distinct clinical entities. There are a multitude of clinical conditions without thrombocytopenia to cause recurrent symptoms of red, swollen, and burning pain in the feet or hands. These other forms are referred to as secondary erythralgia and may originate from a side effect of drugs or arise from various disorders.³² In contrast to primary erythralgia, the secondary forms arise at an adult age. We have demonstrated that the calcium antagonist verapamil may cause secondary erythralgia.⁴⁰ Other vasoactive drugs such as nifedipine, nicardipine, pergolide, and bromocriptine have been shown to elicit secondary erythralgia.^{40,41} Treatment consists of stopping the causative drug. Other conditions associated with secondary erythralgia include cutaneous vasculitis, vasculitis in systemic lupus erythematosus, hypertension, and rheumatoid arthritis.^{42,43} Among 11 cases of painful, burning extremities, described by Babb and Allen, six were secondary to hypertension, two to diabetes mellitus, and one case each to venous insufficiency, systemic lupus erythematosus, and rheumatoid arthritis. Nowadays, these cases can be classified as secondary erythralgia. Therapy of the underlying disorder is associated with cure of secondary erythralgia.

CONCLUSIONS

A categorization of entities is mandatory in medicine, especially when it comes to the interpretation of clinical data from patients with red, warm, and swollen extremities.⁴⁴ Based on extended experiences and detailed documentation of typical patients and on a careful review of the literature, we are able to present a sound classification of the whole clinical spectrum of red, burning, painful, and congested extremities described by Mitchell (Table 1). Erythromelalgia is restricted to thrombocytopenia of various myeloproliferative disorders. Primary erythralgia is a mysterious congenital disorder of elusive pathophysiology. Secondary erythralgia is associated with a detectable underlying disorder, vasculitis in particular, or is a side effect of vasoactive drugs. Applying the proposed criteria for these three separate and distinct disorders facilitates the interpretation of results from present and future studies.

DRUG NAMES

bromocriptine mesylate: Parlodel
nicardipine hydrochloride: Cardene
nifedipine: Adalat, Procardia
pergolide mesylate: Permax
verapamil: Isoptin

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