Coexistence of erythromelalgia and Raynaud's phenomenon.

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Erythromelalgia is characterized by spontaneous recurrent episodes of redness, heat, and pain of the extremities that can be triggered or worsened by heat. Raynaud's phenomenon occurs in response to cold exposure and presents as pallor of the fingers or toes, often followed by cyanosis and rubor. Although the 2 conditions may appear to be opposites in symptomatology and clinical presentation, there are very rare reports of their coexistence. A case of coexistent erythromelalgia and Raynaud's phenomenon is presented. The pathophysiology is reviewed to elucidate a common mechanism underlying some cases of the 2 seemingly opposite conditions. A review of the literature indicates that causative and pathophysiologic similarities between the 2 conditions may exist in some cases. Rare reports of coexistence of the 2 disease processes further strengthen such research findings. (J Am Acad Dermatol 2004;50:456-60.)

Erythromelaigia (EM) is a rare syndrome, first described by Mitchell in 1878(1), which is characterized by recurrent episodes of bilateral redness, heat, and pain, usually arising in the lower extremities, less commonly in the upper extremities, nose, and ears (2). Although occasionally referred to as erythermalgia(3), "erythromelalgia" is the more commonly used name for the condition.

In 1862, Raynaud first described the phenomenon that still carries his name(4). Attacks lasting from a few minutes to several hours are most commonly set off by exposure to cold or emotional distress and consist of pallor, sometimes followed by cyanosis and rubor of fingers and less commonly of toes, nose, and ears.

Whereas the symptomatology of EM is often considered to be the opposite of that of Raynaud's phenomenon (RP), there are very rare reports of both conditions coexisting in the same patient(5-8). We present a new case of such coexistence and review the literature on the pathophysiology of the 2 disorders.

CASE REPORT

A 42-year-old French Canadian woman presented with a 4-year history of recurrent attacks of painless

symmetric pallor involving 10 toes, distal metatarsal regions, and 4 fingers on each hand, while sparing the thumbs. The attacks were precipitated by exposure to cold, but not by emotional stress. After the pallor, fingers and toes would become cyanotic and, subsequently, intensely red, each attack lasting 10 to 15 minutes.

The patient also reported a 3-year history of recurring bilateral redness, warmth, and burning discomfort, but no pain, in her toes. Symptoms were usually triggered by warm ambient temperatures and were relieved by cooling of the lower extremities. Such attacks were more frequent late in the afternoon, with abatement of symptoms by early morning, and were reported to occur several times a week.

Her medical problems included discoid lupus erythematosus on her nose during the last 4 years and a history of urticaria. She has experienced bilateral knee arthralgias in the last year, but no other symptoms of connective tissue disease (CTD). She denied diabetes, migraines, allergies, symptoms of hypothyroidism, or family history of RP, EM, CTI), or myeloproliferative disorders. She worked as a salesperson with no exposure to repetitive trauma, vibration injury, or polyvinylchlorides. She smoked 1 pack of cigarette and drank 1 glass of wine per day.

On examination, she exhibited no signs of CTD. Peripheral pulses and capillary refill time were normal, as were the Allen test and nailfold capillary microscopy. Laboratory investigations, including complete blood cell count, erythrocyte sedimentation rate, antinuclear antibody titer, rheumatoid factor, complement levels, VDRL, liver function tests, uric acid, glucose, and urinalysis were within normal limits. Fasting triglycerides levels were normal, but total and low-density lipoprotein cholesterol levels were mildly increased (5.71 and 3.96 mmol/L, respectively). Chest and hand radiographs were normal.

On the basis of these features, we made a diagnosis of primary RP and primary EM, grade 1 to 2. She was prescribed 2% nitroglycerin cream twice daily to the base of the fingers and toes, and on follow-up visit her symptoms were significantly relieved. However, because of the history of discoid lupus erythematosus and arthralgias, we could not completely rule out secondary RP or EM and will continue to carefully monitor the patient.

DISCUSSION

Erythromelalgia

Acute attacks of EM most commonly occur late in the day, last through the night, and may impair sleep .2 Symptoms usually abate by early morning and may, therefore, not be present during a visit to a physician. Attacks may be precipitated or worsened by limb warming, exercise, or dependency of the affected extremity. Severity may range from

very minor discomfort relieved by limb elevation and not requiring limb cooling (grade 1), to very severe continuous burning pain that limits mobility and necessitates around-the-clock cooling with ice water or epidural anesthesia (grade 8).

EM may be primary or secondary. Both forms are more common in girls and women; however, primary EM typically affects younger patients and is more often bilateral and with more widespread involvement(8). Secondary EM is associated with various underlying conditions and can precede them by up to several years(9). Known associated disorders include essential thrombocythemia and polycythemia rubra vera, diabetes, peripheral neuropathy, systemic lupus erythematosus, rheumatoid arthritis, hypertension, frostbite, colon carcinoma, and gout (8-12), and administration of calcium channel blockers or bromocriptine (13,14). Of interest to the current case, the series by Kalgaard et al(8) included 1 patient with discoid lupus erythematosus, although the association was most likely coincidental.

The differential diagnosis of EM includes peripheral neuropathies, reflex sympathetic dystrophy, nerve compression, plantar neuroma, chronic venous insufficiency, occlusive vascular diseases such as thromboangiitis obliterans, and Fabry's disease and mercury poisoning in children (9,10,15).

Once the diagnosis of EM is made, it is important to differentiate between primary and secondary forms and to treat, if possible, the underlying cause of secondary EM. A workup should commence with a thorough history and physical, including medication history and search for clinical signs of CTD such as digital ulceration, pitting scars over the finger pulp, sclerodactyly, and telangiectases. A complete blood cell count and erythrocyte sedimentation rate should be performed(5). Other investigations, including antinuclear antibodies, rheumatoid factor, complement levels, serum glucose, lipid profile, and liver function tests, should be undertaken if suggested by history or clinical examination.

The choice of treatment for EM depends on the underlying cause of the condition. Patients with myeloproliferative disorders usually respond well to low doses of aspirin, whereas most other patients do not. Depending on the subtype of EM, as described below, vasoconstriction with nonselective (B-blockers or vasodilatation with calcium channel blockers or, in severe cases, prostacyclin may be attempted(11). Care must be taken when initiating therapy for EM. Many of these medications, especially calcium channel blockers, can actually precipitate an acute attack of EM. Other symptomatic treatments may include gabapentin, carbamazepine, venlafaxine, and amitriptyline for pain control, and transcutaneous electrical nerve stimulation(2,11).

Raynaud's phenomenon

RP is much more common than EM. The prevalence of patients who have had at least 1 attack of RP is 5% to 10% of the general population and up to 30% of young women(16). Initial pallor is typically necessary for the diagnosis. Cyanosis alone could represent acrocyanosis(11), although some authors recognize cyanotic RP as a nonclassic form of

the disorder(17). Attacks are usually triggered by cold or emotional stimulus. Although usually a benign condition, with the majority of patients experiencing relatively little or no pain, RP can occasionally result in ulcerations and even dry gangrene.

Like EM, RP can be primary, formerly known as Raynaud's disease, or secondary, formerly known as Raynaud's syndrome. As some underlying conditions, especially progressive systemic sclerosis, may develop up to 5 years after the initial diagnosis of RP(18,19), a classification of "suspected secondary RP" has been proposed(20). These patients display some symptoms of a CTD, but do not satisfy all of the American Rheumatism Association criteria. Such cases warrant extensive workup and regular fol-low-up evaluations.

Primary RP most commonly affects females in the first and second decades, often with a familial history of the disease; is always symmetric; and usually involves fingers and toes, while sparing the thumbs.

Secondary RP is most commonly associated with CTD; other causes include thromboanghtis obliterans, thoracic outlet syndrome, paraneoplastic syndromes, hypothyroidism, and administration of beta-blockers"(18) or ergotamines(15). Occupational causes include exposure to vibrating machinery in the case of vibration white finger disease(18,21), polyvinylchloride(11), or frozen foods(22).

The initial screening of RP should include history, clinical examination, nailfold capillary microscopy, and antinuclear antibody titer. The physical examination should include examination of the peripheral pulses, Allen test (compression of both radial and ulnar arteries in a closed fist, followed by relaxation of the fist and release of one of the arteries to observe palmar flushing and, consequently, arterial patency), and search for signs of CTD or other autoimmune disorders. Capillary microscopy using an ophthalmoscope or a dermatoscope is a quick, simple, inexpensive, and much underused examination. Together, these investigations can identify 96.5% of all secondary cases(23). The addition of chest and hand radiographs for the evaluation of lung fibrosis and subcutaneous calcinosis, respectively, increase this figure to 98.8% (23).

Treatment modalities for RP may vary according to the severity of the disease process. In mild cases, preventive measures, such as heated gloves and socks, may suffice for symptom relief. More severe cases may require vasodilatory medications, most notably calcium channel blockers. In addition, prostaglandin infusions and lower limb sympathectomy have been successfully used in very severe disease (11).

Review of pathophysiology of EM and RP

Although some authors believe that the coexistence of EM and RP is simply coincidental(8), recent research points to a possible connection between the 2 conditions. Cutaneous circulation is subdivided into 2 compartments. Less than 20% of cutaneous blood supply passes through the capillaries, where metabolic exchange takes place, whereas more than 80% is diverted into arteriovenous (AV) anastomoses that are

responsible for hemodynamic and thermal regulation (15). Such anastomoses are most prevalent in the hands, feet, nose, and ears, thus, corresponding to the areas most commonly affected by both EM and RP. Under normal circumstances, AV anastomoses constrict in a cold environment and dilate in a hot one.

The pathophysiology of RP has been elusive. It is currently believed that the initial pallor is caused by a cold or emotion-induced constriction of AV anastomoses, followed by venous stasis during the cyanotic phase and reactive vasodilatation during the rubor phase(24). Triggers for the initial vasospasm may vary among patients; theories include neural signals, cytokines, hormones, and blood- and endotheliumderived chemical mediators(25). Cold increases the affinity of a2-adrenergic receptors(26), and patients with RP have an increased density of these receptors in their digital vasculature(27). However, the administration of selective a1- and a2 antagonists has produced contradictory results (28,29). An alternative neurogenic explanation involves a deficiency of calcitonin gene-related peptide. The number of neurons responsible for the release of this vasodilatory peptide has been shown to be reduced in the skin of patients with RP(30).

In secondary RP, a decrease in the intraluminal pressure from arteriolar occlusion, such as occurs in arteriosclerosis or CTD, is thought to predispose digital microvasculature to vasospasms(24). In addition, prostacyclin, von Willebrand factor, endothelin, thromboxane(11), and endothelium-derived nitric oxide(25) have been found to be abnormal in the secondary form of the disorder, although these might be secondary to platelet or endothelial damage (11,25). Other hypotheses involve nonadrenergic neurogenic mechanisms with consequent impaired vasodilatation(31,32) and endothelial damage secondary to repeated ischemic and reperfusion injury(25).

The pathophysiology of EM has also proved elusive and may vary among patients. Smith and Allen(3) first suggested involvement of AV anastomoses, when they observed that the oxygen content of venous blood from the extremities of patients approached that of their arterial blood. Proposed mechanisms of such AV shunting include neurogenic factors(33,34); inflammatory mediators such as prostaglandin E1(35); abnormal response to vasoconstrictors; and capillary or precapillary obstruction resulting from platelet proliferation or aggregation, hyperviscosity, or arteriosclerosis(33).

According to Kvernebo(36), inadequate nutritive perfusion of skin secondary to increased blood flow through thermoregulatory AV shunts causes tissue hypoxia. Subsequent arteriolar dilatation increases skin temperature, tissue metabolism, and oxygen consumption. Increased local metabolism may account for the occasional elevation of limb temperature above core temperature(37). Furthermore, increased metabolism and oxygen consumption may result in hypoxic injury, with subsequent reduction of sympathetic innervation, receptor hypersensitivity, and increased response to vasoactive mediators(34,38). Postganglionic sympathetic dysfunction is evidenced by abnormal electromyographic recordings and reduced laser Doppler flowmetry signal after reflex sympathetic stimulation(39,40). Therefore,multiple pathophysiologic mechanisms in addition to shunting may contribute to the clinical presentation of EM(41).

Recent research findings by Littleford et al(42) may provide an explanation for the rare instances of coexistence of EM and RP, such as described in this case. In their study, Littleford et al(42) noted lower morning basal temperature in the skin of some patients with EM, indicating increased basal tone in the cutaneous vasculature. The authors hypothesized that many cases of EM are due to morning basal vasoconstriction followed in the afternoon or the evening by reactive hyperemia similar to the rubor phase of RP. This may account for those cases of EM that show diurnal variation in symptomatology. In addition, they postulated that the initial vasoconstriction may be a result of structural alterations in the vascular smooth muscle and the endothelium, amplified response to vasoactive mediators, or primary vasospasm as in RP(42). After capillary vasoconstriction, affected ischemic cells switch to anaerobic respiration, producing a buildup of inflammatory chemicals responsible for opening of AV anastomoses and for pain perception(11). The finding of initial vasoconstriction also helps to explain the therapeutic response of some cases of EM to calcium channel blockers, similar to RP.

The vasoconstriction model of EM does not, however, account for those patients who remain dilated 24 hours a day. As described earlier, calcium channel blockers have precipitated acute episodes of EM in such patients, and warm ambient temperature, a vasodilator, worsens all forms of EM. Belch(11) proposed that at least 2 different types of EM may exist, vasoconstrictive and vasodilatory. Consequently, the choice of vasodilatation or vasoconstriction, respectively, for the treatment for EM may depend on the clinical subtype of the disorder in an individual patient. Vascular studies conducted in warm and cool environments help to differentiate between these 2 subtypes.

Although the pathophysiologic mechanisms underlying both RP and EM are still poorly understood, recent research provides important clues to an occasional convergence of the 2 conditions, as represented by cases of mutual occurrence. In such cases, the initial event underlying both primary EM and primary RP seems to be vasospasm secondary to anatomic or physiologic defects in the innervation, musculature, or endothelium of the vasculature. Subsequent to vasoconstriction, reactive hyperemia may occur in both conditions, but is more apparent and longer lasting in EM (2). Similarly, in both secondary EM and secondary RP, a vasospasm may in some cases be triggered by an obstructive disease or microvascular ischemia and be followed by reactive hyperemia. Further research is needed for a more complete understanding of the pathophysiology and, subsequently, management of the 2 conditions.

REFERENCES

1. Mitchell SW. On a rare vasomotor neurosis of the extremities, and on some maladies with which it can be confounded. Am 1 Med Sci 1878;76:2-36.

2. Cohen JS. Erythromelalgia: new theories and new therapies. J Am Acad Dermatol 2000;43:841-7.

3. Smith LA, Allen EV. Erythermalgia (erythromelalgia) of the extremities: a syndrome characterized by redness, heat, and pain. Am Heart J 1938;16:175-88.

4. Raynaud M. De I'asphyxie et de la gangrene symetrique des extremites [doctoral thesis]. Paris: Rignoux. 1862.

5. Lazareth I, Fiessinger JN, Priollet P. L'erythermalgie, un acrosyndrome rare: treize observations. Presse Med 1988;17:2235-9.

6. Slutsker GE. Coexistence of Raynaud's syndrome and erythromelalgia. Lancet 1990;335:853.

7. Sunahara 1F, Gora-Harper ML, Nash KS. Possible erythromelalgia-like syndrome associated with nifedipine in a patient with Raynaud's phenomenon. Ann Pharmacother 1996;30:484-6.

8. Kalgaard OM, Seem E, Kvernebo K. Erythromelalgia: a clinical study of 87 cases. J Intern Med 1997;242:191-7.

9. Babb RR, Alarcon-Segovia D, Fairbaim JF II. Erythermalgia: review of 51 cases. Circulation 196429:136-41.

10. Drenth JP, Michiels JJ, Van Joost T, Vuzevski VD. Secondary erythermalgia in systemic lupus erythematosus. J Rheumatol 1993;20:144-6.

11. Belch JJF. Temperature-associated vascular disorders: Raynaud's phenomenon and erythromelalgia. In: Tooke JE, Lowe GOO, editors. A textbook of vascular medicine. London: Arnold; 1996. p. 329-52.

12. Markel J. Erythromelalgia: a report of a case of its association with chronic gout with relief of symptoms for two years after intravenous administration of typhoid vaccine. Arch Dermatol 1938;38:73-4.

13. Brodmerkel G1. Nifedipine and erythromelalgia.Ann Intern Med 1983;98:415.

14. Eisler T, Hall RP, Kalavar KAR, Calne DB. Erythromelalgia like eruption in Parkinsonian patients treated with bromocriptine. Neurology 1981;31:1368.

15. Soul ier-Parmeggiani L. Les acrosyndromes vasculaires. Rev Med Suisse Romande 1998;118:839-45.

16. Fitzgerald O, Hess EV, O'Connor GT, Spencer-Green G. Prospective study of the evolution of Raynaud's phenomenon. Am J Med 1988;84:718-26.

17. Andreozzi GM, Signorelli S, Monaco S, Martini R, Ferrara M, Palazzo V. Le phenomene de Raynaud cyanotique: unite semeiologique particuliere. J Mal Vasc 1988;13:179.

18. Priollet P, Vayssairat M, Housset E. How to classify Raynaud's phenomenon: long-term follow-up study of 73 cases. Am J Med 1987;83:494-8.

19. Harper FE, Maricq HR, Turner RE, Lidman RW, LeRoy EC. A prospective study of Raynaud's phenomenon and early connective tissue disease: a five-year report. Am J Med 1982;72:883-8.

20. Kallenberg CG, Pastoor GW, Wouda AA, The TH. Antinuclear antibodies in patients with Raynaud's phenomenon: clinical significance of anticentromere antibodies. Ann Rheum Dis 1982;41: 382-7.

21. Belch JJF. Raynaud's phenomenon. Curr Opin Rheumatol 1990; 2:937-41.

22. Mackiewica SJ, Piskorz M. Cold injury in frozen food handlers. J Cardiovasc 1977;18:151-4.

23. Priollet P, Yeni P, Vayssairat M, Segond P, Tallon F, Housset E. Bilan 6tiologique minimum des phenomenos de Raynaud: cent deux cas. Presse Med 1985;14:1999-2003.

24. Priollet P, Lazareth I. Acrosyndromes vasculaires. Agressologie 1990;31:212-8.

25. Wigley FM, Flavahan NA. Raynaud's phenomenon. Rheum Dis Clin North Am 1996;22:765-81.

26. Flavahan NA, Lindblad LE, Verbeuren T1, Shepherd JT, Vanhoutte PM. Cooling and alpha 1- and alpha 2-adrenergic responses in cutaneous veins: role of receptor reserve. Am J Physiol 1985;249:H950-5.

27. Coffman JD. Raynaud's phenomenon: an update. Hypertension 1991;17:593-602.

28. Freedman RR, Baer RP, Mayes MD. Blockade of vasospastic attacks by alpha 2-adrenergic but not alpha 1-adrenergic antagonists in idiopathic Raynaud's disease. Circulation 1995;92:144851.

29. Cooke 1P, Creager SJ, Scales KM, Ren C, Tsapatsaris NP, Beetham WP Jr, et al. Role of digital artery adrenoceptors in Raynaud's disease. Vasc Med 1997;2:1-7.

30. Bunker CB, Terenghi G, Springall DR, Polak JM, Dowd PM. Deficiency of calcitonin gene-related peptide in Raynaud's phenomenon. Lancet 1990;336:1530-3.

31. Khan F, Coffman JD. Enhanced cholinergic cutaneous vasodilation in Raynaud's phenomenon. Circulation 1994;89:1183-8. 32. Smith PJ, Ferro CJ, McQueen DS, Webb DJ. Impaired cholinergic dilator response of resistance arteries isolated from patients with Raynaud's disease. Br J Clin Pharmacol 1999;47: 507-13.

33. Zoppi M, Zamponi A, Pagni E, Buoncristiano U. A way to understand erythromelalgia. J Auton Nerv Syst 1985;13:85-9.

34. Uno M, Parker F. Autonomic innervation of the skin in primary erythromelalgia. Arch Dermatol 1983;119:65-71.

35. Jorgensen HP, Sondergaard J. Pathogenesis of erythromelalgia. Arch Dermatol 1978;114:112-4.

36. Kvernebo K. Erythromelalgia-a disease caused by microvascular shunting. Vasa 1998;51(Suppl):1-40.

37. Sandroni P, Davis MDP, Harper CM, Rogers RS, O'Fallon WM, Rooke TW, et al. Neurophysiologic and vascular studies in erythromelalgia: a retrospective analysis. J Clin Neuromuscular Dis 1999;1:57-63.

38. MorkC, Asker CL, Salerud EG, Kvernebo K. Microvascular arteriovenous shunting is a probable pathogenetic mechanism in erythromelalgia. J Invest Dermatol 2000;114:643-6.

39. Davis MDP, O'Fallon WM, Rogers RS, Rooke TW. Natural history of erythromelalgia-presentation and outcome in 168 patients. Arch Dermatol 2000;136:330-6.

40. Mork C, Kalgaard OM, Kvernebo K. Impaired neurogenic control ofskin perfusion in erythromelalgia. J Invest Dermatol 2002;118: 699-703.

41. Davis MDP, Rooke TW, Sandroni P. Mechanisms other than shunting are likely contributing to the pathophysiology of erythromelalgia. J Invest Dermatol 2000;115:1166.

42. Littleford RC, Khan F, Belch JJF. Skin perfusion in patients with erythromelalgia. Eur J Clin Invest 1999;29:588-93.