Unexpected healing of cutaneous ulcers in a short child (with erythermalgia).

by Rolando Cimaz Roberto Rusconi, Emilio Fossali, Paolo Careddu

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A boy aged 10 years was referred to the Pediatric Department of Milan University Hospital, Milan, Italy, with a long history of pain in the lower limbs, alleviated only by exposure to cold. His legs were swollen, with multiple cutaneous ulcers. He had severe painful crises, and was totally Incapacitated. After the diagnosis of erythermalgia was made, numerous treatments were tried, but none were successful. After finding growth hormone (GH) deficiency, we started treatment with recombinant GH. He had immediate relief of pain and complete healing of ulcers. We postulate that the healing of the ulcers can be attributed to the GH-promoting effect on dermal connective tissue. Lancet 2001; 358:211-12

A Philipino boy aged 3 years, with no family history of leg ulcers, started to complain of burning pain in the lower limbs, which was aggravated by heat. Occasionally, a milder pain was present in the hands as well. From the age of 9 years the pain became more severe, and trophic changes in the feet began to appear. He was admitted to different hospitals seven times, and many tests were done, none of which were conclusive. The first diagnosis was reflex sympathetic dystrophy, but when we saw him at 10 years of age in the pediatric Department of Milan University Hospital, Milan, Italy, we thought that erythermalgia-a syndrome of red, warm, and burning extremities-seemed more likely. His lower limbs were oedematous from the knees down, almost cyanotic on occasions; multiple necrotic ulcers were present on both legs and feet (figure A). He gained relief from pain only with immersion of the feet in ice or cold water, or when exposing the limbs to an air conditioner or a fan. He had developed hypertension 1 year before admission to our unit: his blood pressure was consistently around 150/100 min Hg, but increased to 180/120 mm Hg, during painful crises. A biopsy sample from a necrotic lesion of the lower limbs showed evidence of leucocytoblastic vasculitis with sub-occlusion from endothelial hyperplasia. Treatment with corticosteroids brought only mild and temporary relief. Other treatment options included aspirin, diuretics, calcium-channel blockers, ct-blockers and P-blockers, angiotensin-converting-enzyme inhibitors, nitroprusside, prostacyclin and various analgesics, including opioids. Nothing seemed to work during the painful crises, which occurred several times a day and made him wheelchair-bound and unable to go to school.

During a hospital admission at age 12 years, investigations for short stature (119 cm; -

4.5 SD) and reduced growth velocity (<2 cm over the preceding year) showed evidence of growth hormone (GH) deficiency (mean GH concentration during spontaneous nocturnal secretion 1-77 ng/mL, reference value >3-5 ng/mL, with no peaks >5 ng(mL). Concentrations of insulin-like growth factor-1 (IGF-1) concentrations were also reduced (96 ng/mL). Magnetic resonance imaging of the brain showed abnormalities of the pituitary stalk, a small adenohypophysis, reduced depth of the sella turcica, and no evidence of a neurohypophysis. Replacement therapy with recombinant human GH was started shortly after discharge (4-2 U/day subcutaneously 6 days/week). The ulcers healed within 1 month (figure B), and growth velocity improved in the following months. After starting GH treatment, painful crises and hypertensive spikes ceased. However, he continued to take labetalol to keep his baseline blood pressure under control. After 14 months he had no ulcerative lesions or painful crises.

Erythermalgia is a rare syndrome which presents with painful, burning, red, and swollen extremities, relieved by exposure to cold.1 Erythermalgia can be primary, or secondary to autoimmune disorders or thrombocythemia (the latter form is often referred to as erythromelalgia). The primary form can be sporadic or familial, and the disease-susceptibility gene has been localized on chromosome 2g31-32.[2] This child had no family history of suggestive symptoms.

The pathogenetic mechanism of erythermalgia is not precisely known, but it is thought that functional vascular abnormalities might have a role, with a maldistribution of perfusion in favor of arteriovenous anastomoses, increased vascular tone, and possible hypoxic injury to the microvasculature. Hypertension can complicate the clinical course, especially in children.[3] There is no effective treatment for this condition, and the disease can be unrelenting, with most individuals having symptoms for many years.[3] Prolonged exposure to cold and immersion in water can lead to maceration and infection, ultimately requiring amputation in some cases. Sympathetic blockage and epidural infusions have been suggested, but lack of response can be frustrating and some patients have such severe and drug-resistant symptoms that they can cause depression and even suicide. Because all treatments failed before GH replacement in this child and the initiation of GH therapy corresponded with the healing of ulcers, we suggest a causal role for GH, a known mitogen for fibroblasts

The wound-healing properties of GH result from its growth-promoting effect on dermal connective tissue, mediated by the autocrine and paracrine action of insulin-like growth factor (IGF)-l.[4,5] In particular, in the wound microenviromental IGF-1-system, IGF-1 can directly stimulate epidermal and dermal cells, because of its capacity to induce protein-DNA synthesis and proliferation.

Indeed, a significant increase in concentrations of IGF-1 and its receptors has been described in children with burns treated with GH, both systemically and at the wound site.[5] In the same study, healing times in patients treated with GH were significantly decreased compared with patients receiving placebo. In the group treated with GH, concentrations of laminin, collagen, and cytokeratin also increased significantly.

This child had unexpected benefit from GH treatment, which could be extended to

other refractory ulcerative lesions.

1. Kurzrock R, Cohen PR. Erythromelalgia: review of clinical characteristics and pathophysiology. Am, f Med 1991; 91: 416-22.

2. Drenth JPH, Finley WH, Breedveld GJ, et al. The primary erythermalgia-susceptibility gene is located on chromosome 2g3l-32. Am, f Him; Genet 2001; 68:1277-82.

3. Drenth JPH, Michiels J, 0zsoylu S. Acute secondary erythermalgia and hypertension in children. Eur J Pediatr 1995;154: 882-85.

4. Ramirez RJ, Wolf SE, Herndon DN. Is there a role for growth hormone in the clinical management of burns injuries? Growth Ham: IGF-1 Res 1998;8:99-105.

5. Herndon ND, Hawkins HK, Nguyen TT, Pierre E, Cox R, Barrow RE. Characterization of growth hormone enhanced donor site healing in patients with large cutaneous burns. Anna Surg 1995; 221: 656-59.

Pediatric Department, WP and University of Milano,
Vie Commends 9, 20= Milano, Italy (Rolando Cimaz MD, Roberto Rusconl MD, Emilio Fossall MD, Paolo Careddu MD)
Correspondence to: Dr Rolando Cimaz