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Case reports

Recombinant granulocyte-macrophage colony-stimulating factor in the treatment of indolent ulcers with Klippel-Trénaunay-Weber syndrome: a case report

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Abstract Klippel-Trénaunay-Weber syndrome (KTWS) is a rare congenital disease characterized by cutaneous hamangiomata, venous varicosities and osseous soft tissue hypertrophy of the affected limb. We report a case of a patient with KTWS who had developed severe chronic, non-healing cutaneous ulcers resulting from several angiography procedures with embolization by various agents. The ulcers were treated with perilesional granulocyte-macrophage colony-stimulating-factor (GM-CSF) with gratifying results. This case report suggests that GM-CSF may enhance the healing of chronic wounds not responding to other treatment modalities in patients with congenital angiodystrophy syndromes, thus salvaging a limb from amputation.

Klippel-Trénaunay-Weber syndrome (KTWS) or angio-osteohypertrophy syndrome is a rare congenital disease described by Klippel and Trénaunay in France [1] at the beginning of the 20th century and by Weber in England [2] a few years later. The disease is characterized by the triad of varicose veins, cutaneous hemangiomas, and hypertrophy of soft tissue and bone. Generally, only one limb is affected, but there are reports of multiple-limb pathology. The leg is the most common site followed by the arms, trunk, and, rarely, head and neck [3,4]. Hemangioma often overlies the vascular malformation and is noted on the lateral aspect of the limb. Complications of hemangiomas include aseptic cellulitis and ulceration, bleeding, and secondary infection, and could be potentially difficult to treat [5]. We report a case of a patient with KTWS who had such severe, chronic, nonhealing cutaneous ulcers that amputation was recommended but was not carried out because of the family's religious beliefs. With family consent and due institutional review board approval, we treated the ulcers with perilesional granulocyte-macrophage colony-stimulating factor (GM-CSF) with gratifying results.

1. Case report

The patient was a 12-year-old African American girl with KTWS. She had debilitating problems with her right leg as a result of this disease. Her right leg had complete arteriovenous (A-V) malformation and was much larger than her left leg. Because of the large A-V malformation, she had been in a state of high-cardiac-output heart failure since

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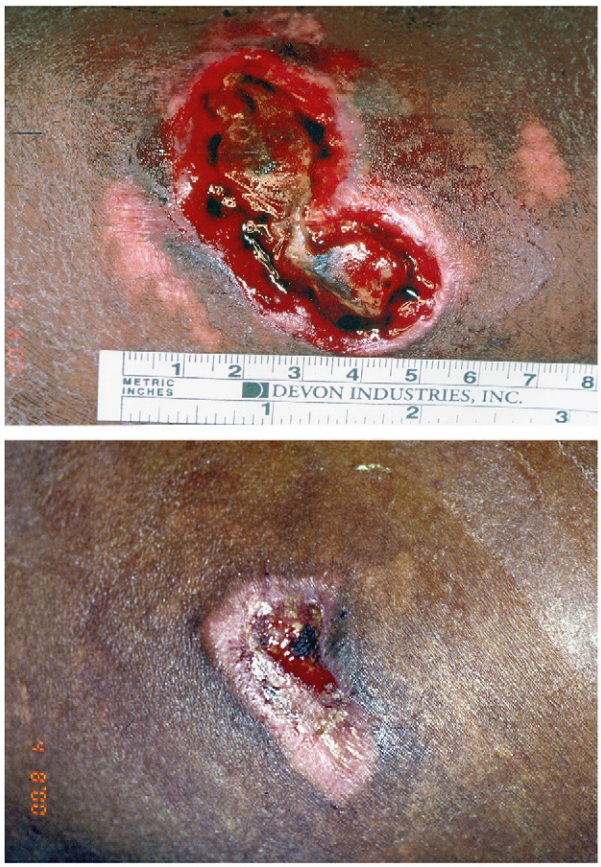
infancy, requiring digitalis and diuretic treatment. In an effort to reduce the blood flow to the leg, she had undergone approximately 10 angiography procedures with embolization by various agents. None of these procedures had been very effective in decreasing the blood flow into the leg. Her most recent embolization involved use of absolute alcohol and coils, and she developed large cutaneous bleeding ulcers on her right thigh and dry gangrene of her right great toe. These ulcers overlay the hemangiomatous lesions, bled frequently, and required compression for several days to achieve hemostasis. The ulcers also required compression on a daily basis. Because the cutaneous ulcers were extensive and failed to respond to conservative treatment and embolization, amputation was considered after 9 months of failed healing. Complicating matters, the family were devout Jehovah's Witnesses and would not allow blood transfusion, which rendered amputation nearly impossible. Therefore, the ulcers were continued to be managed supportively with antibiotics, hyperbaric oxygen, prednisone, dapsone, whirlpool therapy, and glycerin-impregnated dressings.

Based on our prior successful experience in using GM-CSF in common variable immunodeficiency disease ulcers, we decided to treat the patient's ulcers with GM-CSF. After appropriate parental consent and the institutional review board's approval, treatment with GM-CSF was started. At initiation of treatment, the total surface area of the 2 ulcers was 33 cm^2 on the right leg. Before administration of medication, complete surgical debridement of the target ulcers was performed. On the first day of treatment, the GM-CSF solution (500 μg total dose) was injected in small portions (approximately 4 to 8) within the margin of the ulcer to establish tolerability. Each treatment session was spaced approximately 5 to 7 days apart. A total of 12 such treatment sessions were conducted, and at each session, careful evaluation of the ulcers was done. The ulcer dimensions were recorded by using geltrate acetate tracing. Evidence of healthy granulation tissue started to appear within 2 to 3 days of treatment initiation. Healing started from the periphery and from within the ulcer bed at sites of GM-CSF injections (see pictures). The total dose of GM-CSF was adjusted at each individual treatment session depending on the size of the ulcer, and the dose given perilesionally ranged between 500 and 2000 μg divided into smaller aliquots as needed. During a period of 3 months, all ulcers were completely healed. No recurrences or infection of the treated ulcers was reported. All intra- and intertreatment sessions were well tolerated by the patient and the peripheral white blood cell counts remained in the reference range. Almost 5 years after GM-CSF therapy the patient's ulcers remain healed, and she has not reported any adverse events during and after therapy.



2. Discussion

The etiology of KTWS is unknown. Manifestations of the syndrome begin at birth or shortly after, with most patients displaying cutaneous hemangiomas of the port wine type. The patient presented in this report had developed chronic ulcers resulting from repeated measures of embolization with various agents to reduce concomitant systemic complications. The ulcer became a persistent source of pain and potential site for infection. To avoid amputation, this patient was given a novel therapy.

The use of GM-CSF has been described in the treatment of cutaneous ulcers of different etiologies, including diabetic foot ulcers [6], venous stasis ulcers [7], pressure ulcers [8], surgically induced chronic wounds after radiotherapy [9], doxorubicin-induced tissue necrosis [10], and extensive leg ulcers [12]. Recent reports have shown GM-CSF has a role in wound healing [13]. Marques da Costa et al [14] conducted randomized, double-blind, placebo-controlled, dose-ranging studies in 60 patients with chronic venous ulcers. The number of healed wounds in the placebo and the treated arms were significantly different (P = .05), with 4 (19%) of 21 patients in the first group having healed at week 13 compared with 12 (57%) of 21 and 11 (61%) of 18 patients in the 200- and the 400-μg groups, respectively. There were only minor side effects attributable to the treatment. However, reexamination after 6 months showed that none of the treated ulcers recurred during that period.

Several similar studies have also had encouraging results and the doses used have varied between 30 [15] and 400 μg [16,17] and 10 μg cm^{-2}. More recently, some authors have used topical GM-CSF successfully for treating cutaneous ulcers [11,18]. The molgramostim solution appears to be adequate therapy for many leg ulcers. Long-term outcome studies are sparse, with only one study showing good results at 1 year in growth factor–treated pressure ulcers [19].

GM-CSF likely exerts its effects on wound healing through sequential mechanisms involving homeostasis and inflammatory responses that enhance proliferation and activation of neutrophils and monocyte/macrophages leading to increased phagocytic and microbicidal activity. GM-CSF enhances production by macrophages of other cytokines that stimulate wound healing, such as platelet-derived growth factor, angiogenetic factor, interferon γ, a proinflammatory cytokine, and interleukin 6, an essential factor for reepithelialization, and also by increased production of smooth muscle actin in fibroblasts, necessary for granulation tissue formation. Histologically, GM-CSF injection sites reveal epidermal thickening with increased numbers and layers of enlarged keratinocytes with increased expression of "regenerative" epidermal growth proteins. In addition, GM-CSF induces differentiation and proliferation of fibroblasts in human skin tissue.

We used the GM-CSF subcutaneously in doses varying between 500 and 2000 μg in each session divided into small doses and injected into the inner margins of the ulcer. Our patient did not report any adverse event and we did not detect any systemic or peripheral hematologic abnormalities. The treated area continues to be healthy and intact on follow-up of almost 5 years.

The current case is particularly remarkable because of the extent of involvement of the ulcers and the long-term, continued healthy intact skin posttreatment. GM-CSF was well tolerated in this patient despite the use of higher doses. No systemic or local side effects from the therapy were observed. This, in addition to the clinical trials, shows the potential for the use of GM-CSF in the treatment of many different etiologies. Molgramostim is expected to improve the quality of life affected by infection, thereby minimizing the length of hospital stay.

In conclusion, the success observed in this case suggests that GM-CSF may enhance the healing of chronic wounds not responding to other treatment modalities in patients with congenital angiodystrophy syndromes, thus avoiding amputation.

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