Thalidomide for the Treatment of Refractory Necrobiosis Lipoidica

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The Cutting Edge: Challenges in Medical and Surgical Therapeutics

A 51-year-old woman with a 2-year history of biopsy-proved necrobiosis lipoidica (NL) and a 10-year history of recurrent lower limb ulcerations was referred to the dermatology clinic because of a new ulceration on her right lower extremity. At her initial presentation, her physical examination was remarkable for 2 atrophic plaques with active disease and palpable reddish brown borders on her right lower extremity. The larger of the 2 plaques had a 3.0 × 2.0-cm ulceration. The left lower extremity had 3 atrophic plaques with similar palpable reddish brown borders (Figure 1). Although past ulcerations were related to trauma, the patient reported that the new ulcer had developed spontaneously and denied any history of diabetes. Multiple therapies, including intrallesional and topical steroids, pentoxifylline, and compression, had been tried, with only partial healing of the ulceration. Her medical history was unremarkable, with no associated difficulties with blood glucose control and no family history of diabetes. Her medications included cetirizine hydrochloride (Zyrtec), venlafaxine hydrochloride (Effexor), and mupirocin (Bactroban).

We set out to find an effective therapy for our patient’s NL ulcerations. The current treatment for NL is not very satisfactory, as the exact pathogenesis of the disease is unknown. The disease is usually chronic and often progresses to cosmetically unsightly ulcerations and scarring.

After receiving proper counseling about the potential adverse effects of thalidomide therapy, including teratogenicity and risk of peripheral neuropathy, the patient was enrolled in a proprietary education and restrictive distribution program (STEPS [System for Thalidomide Education and Prescribing Safety]; Celgene Corp, Summit, NJ). This program requires that patients must either not be of childbearing potential or use contraception and receive monthly pregnancy tests. Thalidomide can be prescribed for only 28 days at a time, with no refills and with each prescription valid for 1 week. Also, our patient underwent baseline 4-nerve electromyography and a neurologic examination, which were repeated every 6 months thereafter.

Thalidomide therapy was then started at a dosage of 150 mg/d to be taken at night, and compression therapy was initiated on the right lower extremity. After 1 month, the ulceration of the large atrophic plaque on the right lower extremity was approximately 95% epithelialized and all lesions were significantly lighter in coloration, with 50% clearing of 1 superior lesion on the left lower shin area (Figure 2). At 4 months, all lesions were clinically improved, with decreased inflammation, and no new lesions were noted. At that time, the dosage of the thalidomide therapy was lowered to 50 mg/d because of fa-
Necrobiosis lipoidica is an uncommon disease that most frequently develops in the lower extremities.\(^1\) It is 3 times more common in females than males, with an average age at onset of 30 years, although it can occur at any age. It is frequently associated with diabetes (more than 75% of patients with NL either have or will develop diabetes mellitus). However, it is seen in only 0.3% to 0.7% of the entire diabetic population. There is no known relationship between diabetic metabolic control and the severity or progression of NL, which has also been reported without diabetes mellitus in about 25% of patients. The only known risk factor for NL in persons without diabetes is female sex.\(^2\)

Necrobiosis lipoidica is an inflammatory skin disorder of unknown origin. The pathologic changes associated with NL include collagen degeneration with a granulomatous response, thickening of blood vessel walls, and fat deposition. Some leading theories suggest that NL is a cutaneous manifestation of diabetic microangiopathy, an immune complex vasculitis, abnormal production of collagen, or impaired neutrophil migration, leading to increased numbers of macrophages and granuloma formation.\(^3,4\)

Most patients with NL present with asymptomatic shiny patches on the skin that slowly enlarge over time. In most patients, the lesions of NL are multiple and bilateral, maintain a chronic course, and are usually not painful. Also, in most cases, the primary complaint is the poor cosmetic appearance of the skin. The lesions usually are reddish brown initially, found on the lower extremities (15% occur elsewhere), and progress to oval or irregularly shaped indured plaques with central atrophy and yellow pigmentation, with the margins retaining a reddish brown pigmentation. Central telangiectasia may also be seen. Ulcerations typically occur after trauma and are usually associated with pain.\(^2\)

The management of NL includes protection of the leg with elastic stockings and therapy with topical and intralesional steroids, antiplatelet drugs such as aspirin or ticlopidine, and agents that decrease blood viscosity such as pentoxifylline; however, the treatment of the disease remains suboptimal, as most patients show continued slow progression of their disease.

Thalidomide was first used in Europe during the late 1950s as a sedative, with its use quickly expanding to prevent morning sickness in pregnant women. Its use was never approved by the Food and Drug Administration because of concerns about nephrotoxic effects. In 1961, a definite link between thalidomide and its teratogenic effects was established, and it was withdrawn from the European market.

Interest in thalidomide resurfaced in 1965, when Skeskin found it useful in the treatment of erythema nodosum leprosum,\(^5\) which is characterized as a vasculitic complication of leprosy with painful subcutaneous nodules. Thalidomide therapy is currently a first-line treatment for symptomatic, moderate to severe erythema nodosum leprosum.\(^6\)

Thalidomide is an immunomodulatory agent with anti-inflammatory and antiangiogenic properties. The exact mechanism of its actions has not yet been clearly outlined; however, its anti-inflammatory effects are believed to be mediated through suppression of tumor necrosis factor α via degradation of its messenger RNA and by decreasing the ratio of helper T cells to suppressor T cells. Also, its antiangiogenic properties appear to stem from the inhibition of vascular endothelial growth factor and basic fibroblast growth factor.\(^7\)

While the only indication for the use of thalidomide that has been approved by the Food and Drug Administration is for the treatment and suppression of erythema nodosum leprosum, the drug has also been used off-label as an antitumor agent, with some success, as well as in the treatment of Behc¸et disease, pyoderma gangrenosum, chronic discoid lupus erythematosus, lichen planus, prurigo nodularis, sarcoidosis, graft-vs-host disease, human immunodeficiency virus, Jessner lymphocytic infiltration, Langerhans cell histiocytosis, and pemphigoid.\(^8\) The most worrisome adverse effects of thalidomide include teratogenicity, peripheral neuropathy, deep venous thrombosis, somnolence, and, rarely, reversible neutropenia in fewer than 1% of all patients.

Because the teratogenicity of thalidomide can now be avoided through prescription control, peripheral neuropathy is one of the main limiting factors related to its use.\(^7\) Thalidomide neuropathy is usually axonal, bilateral, and symmetrical. Clinical manifestations include symmetrical distal paresthesia with or without sensory loss. Electrophysiologic findings include a sensory axon polynuropathy with a sensory nerve action potential (SNAP) amplitude decrease. A 50% decrease in SNAP amplitude is closely related to clinical signs and symptoms.\(^7,9\) Therefore, it is recommended that baseline nerve studies be performed in all patients who receive thalidomide within 3 months of initiating therapy and every 6 months thereafter. With a decrease in SNAP of greater than 30%, more frequent testing is recommended, and thalidomide therapy should be discontinued if the SNAP decreases by more than 50% until the peripheral neuropathy resolves.\(^7,9\)

Clinical data suggest that thalidomide has a thrombogenic effect at doses higher than 100 mg in patients with multiple myeloma or antiphospholipid syndrome. Somnolence can be managed by lowering the dosage or by prescribing the use of the drug at night. Neutropenia can be measured with a baseline blood cell count and continuous monitoring.\(^5,10\)

Thalidomide represents a possible powerful new drug in the treatment of NL. Its use requires careful monitoring of its main side effects and a careful assessment of
the risk-benefit ratio. This case illustrates the benefits of thalidomide therapy for patients with NL, and further studies are needed to understand the full potential of this unique drug.

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REFERENCES

Submissions
Clinicians, residents, and fellows are invited to submit cases of challenges in management and therapeutics to this section. Cases should follow the established pattern. Manuscripts should be prepared double-spaced with right margins nonjustified. Pages should be numbered consecutively with the title page separated from the text (see Instructions for Authors for information about preparation of the title page). Clinical photographs, photomicrographs, and illustrations must be sharply focused and submitted as separate JPG files with each file numbered with the manuscript number (eg, Fig 1_DCE00001.jpg). Material must be accompanied by the required copyright transfer statement (see Instructions for Authors). Preliminary inquiries regarding submissions for this feature may be submitted to George J. Hruza, MD (ghruza@aol.com). Manuscripts should be submitted electronically to archdermatol@jama-archives.org. Please indicate in your e-mail that the manuscript is a submission to Cutting Edge.

Correction
Error in Byline. In the Evidence-Based Dermatology Study by Charman et al titled “Measuring Atopic Eczema Severity Visually: Which Variables Are Most Important to Patients?” published in the September issue of the ARCHIVES (2003;141:1146-1151), Michael Bigby, MD, was mistakenly added to the byline.