A 39-year-old African American woman was referred in April 1995 with a 1-year history of skin thickening. The process began on her hands and progressed to involve her arms, face, neck, shoulders, chest, and proximal extremities. Her only systemic complaints were limited mobility of her joints, particularly her hands and wrists. Physical examination findings revealed leonine facies. The skin of the neck, shoulders, and chest exhibited 1- to 2-mm coalescent linear papules. The skin of the hands, forearms, upper arms, and trunk was sclerotic. Skin biopsy results showed marked dermal thickening, displacement of collagen bundles by mucin, and numerous spindled fibroblasts, consistent with scleromyxedema. The results of laboratory tests, including a complete blood cell count, chemistry tests, liver function tests, an antinuclear antibody panel, an extractable nuclear antigen panel, and thyroid function tests, were normal. Immunoglobulins were obtained, and the following levels were revealed: IgM, 92 mg/dL (reference range, 25-210 mg/dL); IgA, 152 mg/dL (reference range, 40-390 mg/dL); and IgG, 1490 mg/dL (reference range, 525-1650 mg/dL), with a λ light chain monoclonal gammopathy. Hematologic evaluations, including serum and urine protein electrophoresis, immunoelectrophoresis, a bone marrow examination, and radiography of the head and chest, produced no evidence of multiple myeloma.

Because of significant restriction of joint mobility, the patient underwent treatment with cytotoxic agents. She was initially treated with melphalan, 16 mg/d orally (PO), plus prednisone, 100 mg/d PO, for 4 days at a time in 1-month intervals for 4 cycles from June 1995 to September 1995, with little response. She was then treated with cyclophosphamide, 75 mg/d PO, plus prednisone, 100 mg/d PO, for 21 days at 1-month intervals for 6 cycles from October 1995 to March 1996, with minimal improvement. The patient was then administered prednisone, 40 mg every other day, from April 1996 to June 1996, again with no improvement. A trial of cladribine, 0.1 mg/kg, was instituted for 5 days at 1-month intervals for 5 cycles from September 1995 to January 1997, and was unsuccessful. The patient then received supportive therapy, including topical corticosteroids and emollients, and underwent physical therapy.

In February 1998, the patient developed status epilepticus, fever, and hypotension, requiring admission to the intensive care unit and mechanical ventilation. The findings of an examination for a cause of the patient’s illness, including computed tomography, magnetic resonance imaging, and magnetic resonance angiography of the head, and of a complete infectious disease workup were negative. Because an organic brain syndrome was previously reported in association with scleromyxedema and there was no obvious other cause, this episode was attributed to scleromyxedema. The patient returned to her baseline level of function and was administered phenytoin (Dilantin), topical corticosteroids, and emollients. She declined further chemotherapy because of the lack of efficacy and intolerable adverse effects.

The patient’s disease progressed to her lower extremities. She had difficulty walking and could no longer perform activities of daily living. She developed significant alopecia. The patient was regularly assessed for progression to multiple myeloma. Despite the persistence of the monoclonal gammopathy, she never developed marrow plasmacytosis, lytic bone lesions, or other signs of multiple myeloma. Even with obvious disease progression, further treatment with cytotoxic agents was abandoned because of lack of response and risk of a secondary malignancy.

Because of increasing disability, the patient required further therapy, but alkylating agents had proved ineffective and have unacceptable long-term adverse effects.

The patient began treatment with thalidomide, 100 mg/d PO, in March 2001. Before beginning thalidomide treatment, the patient was registered with the System for Thalidomide Education and Prescribing Safety (STEPS).
In accordance with the STEPS guidelines, the patient was advised to use a barrier form of contraception even though she had a bilateral tubal ligation. The results of baseline pregnancy tests were negative. The results of baseline bilateral electromyography of the lower extremities were normal. She continued undergoing physical therapy and receiving emollients, but was not receiving any other treatment.

The patient tolerated thalidomide well. She experienced mild drowsiness that was minimized with evening dosing, but denied other adverse effects, including paresthesias. The patient returned to the clinic monthly for urine pregnancy tests and refills of thalidomide in accordance with STEPS. She quickly showed signs of improvement. Before starting thalidomide therapy, her IgG level (reference range, 525-1650 mg/dL) was elevated (2338 mg/dL), and 1 month after starting thalidomide therapy, her IgG level decreased to 1952 mg/dL. Within 6 months of starting thalidomide therapy, the patient began to notice decreased thickness of her skin and increased mobility. She became increasingly independent in her daily activities. After 1 year of treatment, the patient began to notice regrowth of her hair (Figure 1 and Figure 2). She has had no difficulty with paresthesias, and electromyography repeated every 6 months has not shown evidence of neuropathy. She has been receiving thalidomide for 1 to 2 years and continues to note improvement in her skin and in the mobility of her joints. Examination of a repeat biopsy specimen after 1 year of treatment with thalidomide showed a significant decrease in mucin (Figure 3 and Figure 4). Her IgG level has steadily increased to 2293 mg/dL, despite continued cutaneous improvement.

**COMMENT**

Scleromyxedema is a disorder of unknown cause, with fewer than 150 reported cases in the literature. It was first described by Dubreuilh in 1906 and Reitmann in 1908. In 1953, Montgomery and Underwood classified papular mucinosis into 4 clinical forms: a generalized lichenoid form, a discrete papular form, a discrete lichenoid plaque form, and a urticarial plaque form. In 1954, Gottron coined the term *scleromyxedema* to describe a unique variant of papular mucinosis corresponding to the generalized lichenoid form.

Scleromyxedema is a disorder of adults, usually affecting those between the ages of 30 and 50 years. It affects both sexes equally. Characteristic physical examination findings include 2- to 4-mm linear dome-shaped flesh-colored papules that coalesce into plaques. The lesions are symmetric and most commonly affect the dor-
Scleromyxedema remains a therapeutic challenge. Reported treatments include dermabrasion, psoralen–UV-A, systemic retinoids, and corticosteroids. Other reports of successful treatment include granulocyte colony-stimulating factor, plasmapheresis, external beam irradiation, intravenous immunoglobulin, interferon alfa-2a, and extracorporeal photopheresis. Multiple chemotherapeutic agents have been used, including melphalan, cyclophosphamide, cladribine, cyclophosphamide, methotrexate, and chlorambucil. Despite all these reported trials, most patients with scleromyxedema do not show a significant response to therapy. The use of these chemotherapeutic agents is limited by toxicity and numerous adverse effects.

It is thought that in patients with scleromyxedema and plasma cell dyscrasia there might be a link with multiple myeloma. This theory is based on the use of alkylating agents. Therefore, the purpose of using chemotherapeutic agents is to disrupt the plasma cell dyscrasia and monoclonal gammopathy. Although the relationship between these disorders is uncertain, scleromyxedema responds to antimetabolites, especially melphalan. In some cases, treatment with melphalan has resulted in the disappearance of the monoclonal protein, with improvement of the skin condition. However, other studies have shown clinical improvement with a variable effect on the immunoglobulin levels. Unfortunately, the use of these medications increases the risk of secondary malignancies, hematologic abnormalities, and sepsis.

We chose thalidomide after its reported success in treating multiple myeloma. We theorized that, like melphalan, which is also used in patients with multiple myeloma, thalidomide might also be effective in patients with scleromyxedema. Thalidomide has been used to treat patients with refractory and relapsed multiple myeloma. Thalidomide also disrupts the plasma cell dyscrasia.

Thalidomide is US Food and Drug Administration approved for the treatment of erythema nodosum leprosum, but given its history of teratogenicity, its use is tightly regulated. In the United States, it is only available through physicians registered with Celgene Corporation (Warren, NJ) and the STEPS program. The STEPS program is designed to prevent pregnancy in patients receiving thalidomide and requires intensive contraceptive counseling, monthly pregnancy tests, and telephone surveys. Thalidomide can also cause drowsiness, dizziness, constipation, amenorrhea, and potentially irreversible sensory neuropathy. It is recommended that patients receiving thalidomide undergo baseline and biannual nerve studies to monitor for the development of neuropathy.

The mechanism of action of thalidomide is unknown. It has immunomodulatory, anti-inflammatory, neural, and vascular effects. Thalidomide exhibits specific inhibition of tumor necrosis factor α. Humoral immunity is affected, as shown by the suppression of interleukin 12.
and the simultaneous enhancement of interleukins 4 and 5 with interferon γ inhibition. It has also been shown to decrease neutrophil chemotaxis and phagocytosis and monocyte phagocytosis. Thalidomide has also been shown to inhibit angiogenesis by an unknown mechanism. The study by Verheul and colleagues also showed inhibition of carcinoma growth in rabbits. This property may allow its use as an antineoplastic agent. It is possible that thalidomide might inhibit the circulating factor that stimulates fibroblast production, thus reversing the progression of scleromyxedema.

We believe that the use of thalidomide was justified in our patient because of a possibly related seizure disorder, progressive disability, and lack of response to other accepted therapies. Her response to thalidomide was dramatic. Thalidomide might represent an effective treatment option in patients with scleromyxedema, and further study is warranted.

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REFERENCES


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