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Thalidomide Treatment of Prurigo nodularis

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Four patients with classic recalcitrant prurigo nodularis had symptomatic and physical responses to thalidomide with remissions. Three of the four patients had increased IgE levels that decreased during therapy. In two patients, short-term treatment (2 to 3 months) was not sufficient to produce remission, but retreatment was effective. Two patients had long-term remission with more than 6 months of treatment. No significant side effects occurred. *Key words: Atopy; Dermatosis; IgE antibodies; Pruritus; Skin tests.* (Received February 15, 1984.)

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In 1973, Mattos (1) first reported the successful treatment of prurigo nodularis with thalidomide. His first patient had been treated in 1968, and after 15 days of treatment with 300 mg of thalidomide, the patient no longer had pruritus. His second patient was treated with thalidomide for prurigo nodularis of 14 years' duration. Her pruritus disappeared after 21 days of 200 mg of thalidomide a day. After 4 months, her skin lesions had involuted remarkably. Sheskin (2) subsequently reported relief of symptoms and lesions with thalidomide in three patients. Our first case, reported to the South Central Dermatology Society in 1978, confirmed this experience (3). More recently, van den Broek (4) reported a successful short-term experience with thalidomide in one patient with prurigo nodularis. We have now treated four patients with thalidomide, and our experience extends for 4 years. We believe this experience justifies a preliminary report on the effectiveness of thalidomide in this chronic, troublesome dermatosis.

REPORT OF CASES

Case 1

A woman noted gradual development of pruritic nodules on the extremities during a 3-year period that began at age 52. The symptoms were aggravated by hot weather and by stress. The problem was severe enough that she was hospitalized three times for a total of 5 months and given prednisone therapy. Although this relieved some of her inflammatory symptoms, her blood pressure became elevated and treatment with spironolactone with hydrochlorothiazide (Aldactazide) was required. Her history showed only high blood pressure and a colon polyp 12 years previously. She said she had hay fever as a teenager and believed that she was sensitive to dust, weeds, fish, flowers, grain, and plastic. She had received desensitization injections for hay fever for 2 years. She gave a family history of atopy: one daughter had hay fever, and a second daughter had dermatitis of the hands and forearms.

At admission, she had discrete, elevated, hyperkeratotic, nodular lesions, many of which were excoriated at the summit and many of which showed a pigmented surrounding halo. The lesions were present on flexure and extensor surfaces of the arms and legs, the lower abdomen; and the low back. Isolated lesions were found on the shoulders and upper back. The scalp, palms, and soles were not involved.

Biopsy findings were consistent with the diagnosis of prurigo nodularis. Direct immunofluorescence of the biopsy specimen was negative. Intradermal skin tests gave a 2+ response to house dust, orris-root, cattle and cat danders, and kapok. Results of multiple additional intradermal tests to molds,

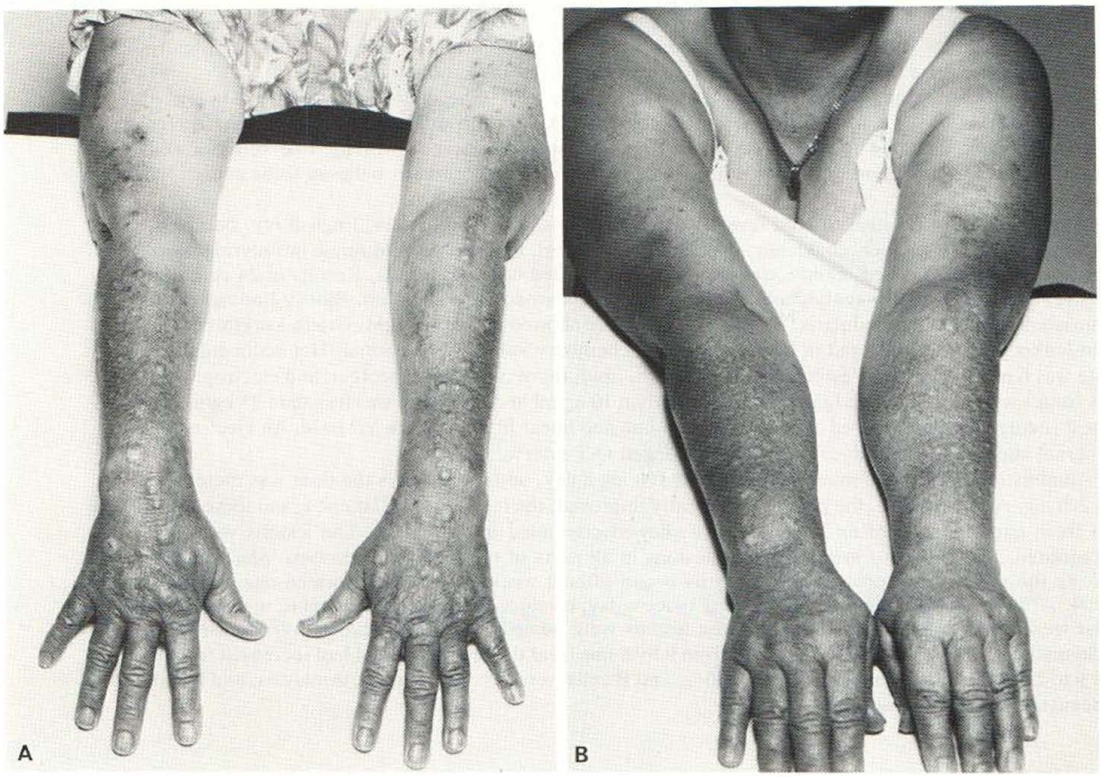

Fig. 1. (case 4). (A) June 1981. Prurigo nodularis lesions on arms. (B) January 1982. Residual lesions after 200 mg of thalidomide daily for 3 months.

trees, and the ragweeds were negative. Delayed hypersensitivity tests were negative to *Trichophyton*, streptokinase-streptodornase, purified protein derivative of tuberculin, and histoplasmin. The reaction to the *Candida* delayed hypersensitivity skin test was 4 mm in diameter. Patch tests to the North American contact group series and preservatives showed only a 2+ reaction at 48 hours to phenylmercuric acetate. The hemogram, blood chemistry, blood lipid, thyroxine, and sedimentation rate values were all normal or negative. The IgE level was 11 860 ng/ml; the other immunoglobulin values were normal. Her total hemolytic complement level was normal. Grade 1–3 leukocytes were found in her urine, from which only normal flora were cultured. On four occasions, the toes and toenails grew *Trichophyton mentagrophytes*. Radioallergosorbent test (RAST) results to cat, dog, house dust, ragweed, June grass, ryegrass, birch, hazel, maple, and beech antigens were two to four times the normal control value.

The patient responded only briefly to triamcinolone, wet dressings, crude coal tar, and ultraviolet light therapy. In May 1977, she began a regimen of 300 mg of thalidomide in 100-mg tablets taken three times a day. One month later, she was having only occasional pruritus. Complaining of nervousness, indigestion, and constipation, she stopped her treatment for 5 days. Subsequently, she began to take 100 mg a day and then took 100 mg twice a day for a week. She thought that some lesions had involuted in this time. After 4 months, the pruritus was less severe; she was now taking one 100-mg tablet a day, having stopped twice-a-day doses because of indigestion and a tired feeling. No itching was present with 100 mg daily. The lesions were flattened, she was sleeping well for the first time in several years, and clearly the involution of the disease was nearly complete.

At the onset of treatment, her IgE level had been 13 360 ng/ml. After 9 months of therapy, the IgE level was 4 802 ng/ml. Four years later, she was still improved, with occasional pruritus.

Case 4

A 59-year-old beautician had typical prurigo nodularis of the arms, legs, and trunk (Fig. 1*A*). It had been present for 7 years and had begun on the back of the hands and arms and on the extensor

surfaces of the arms. In the past 2 years, it had spread widely over the body and now involved both extensor and flexor surfaces. It was aggravated by heat and perspiration. Vitiligo was symmetrically present in the axillae and under the breasts and involved the vulva and perianal area.

The patient had spring hay fever, and her father had hay fever. She said she was sensitive to grass, hay, and flowers. She had had a reaction to tetanus toxoid, with angioedema and dyspnea. Her medical history included the diagnosis of Paget's disease of the spine involving one vertebra and recurrent bladder infection. She gave a history of repeated weed dermatitis believed to be caused by poison ivy.

Patch tests were positive to wild feverfew, carrot, chrysanthemum, dahlia, English ivy, burweed, marsh elder, cedar juniper, cocklebur, dandelion, dog fennel, and fleabane. Multiple intradermal tests to danders, dust, ragweed, molds, trees, and grasses yielded negative results. Results of 24 common RASTs were normal. An acetylcholine intradermal test showed vasodilatation. Biopsy findings were consistent with prurigo nodularis. Immunofluorescence showed cytoids of IgM. Grade 1 erythrocytes and leukocytes were detected in her urine. Blood chemistry values were normal. Her sedimentation rate was 6 mm in 1 hour (Westergren). Hemogram, lipid, thyroxine, serum protein, and electrophoresis values were normal. The IgE value was less than 10 ng/ml and on repeat was less than 25 ng/ml. A chest roentgenogram revealed a calcified granuloma and linear fibrosis in the *left* base. An electrocardiogram showed sinus bradycardia and a prolonged Q-T interval.

Administration of thalidomide was begun at 100 mg a day, and after 3 days the dose was increased to 200 mg. After 1 month, the patient was greatly improved; the lesions were flattened, and there were no fresh excoriations. After 2 months, she showed continued improvement. The lesions were not excoriated, She had no pruritus, and the lesions in all parts of the body had resolved. She stopped taking the medication for 4 weeks; pruritus began after 2 weeks and lesions formed again after 4 weeks. Treatment with thalidomide, 200 mg twice a day, produced remission identical to that with the first treatment course. After 2 months, the lesions were healed (Fig. 1 B). Delayed hypersensitivity skin tests to *Trichophyton* had increased from 9 by 8 mm, and the tetanus toxoid had increased from 9 by 9 to 21 by 20. Circulating T cells were 86%, and B cells were 7%. Hemogram, urinalysis, and blood chemistry values were normal.

LABORATORY STUDIES

Immediate hypersensitivity responses

In case 1, a markedly increased IgE level decreased with therapy. RASTs, in which results were positive to many allergens, were not repeated in this patient. Elevated IgE levels in cases 2 and 3 also were reduced with therapy. The IgE level decreased from 1 434 to 1 091 ng/ml in case 2 and from 3 952 to 1 742 ng/ml in case 3. The IgE levels in case 4 were below 10 ng/ml before and during therapy.

Some intradermal skin tests for immediate sensitivities to dog, cat, cow, rabbit, and hog danders and to ragweeds, house dust, and mixed feathers gave significantly positive results in cases 1, 2, and 3. In case 4, results of immediate sensitive skin tests to 36 antigens were negative and RAST results to 24 allergens were normal.

Cell-mediated responses

Positive patch test results were obtained in cases 1 and 4. The results changed during treatment with thalidomide in case 4. The fragrance mixture that had been negative was 2+ positive at 72 and 96 hours. In addition, four new sensitivities in the weed series were noted, and the 17 reactive patches in

Table 1. *Circulating T and B lymphocytes in prurigo nodularis*

Case	Time of study	T cells, %	B cells, %
2	Posttreatment	78	14
3	Posttreatment	81	1
		89	3
4	Pretreatment	63	22
	After 2 months	90	5
	After 3 months	84	9
	After 1 month of retreatment	86	7

the series of 31 weeds tested were upgraded from 1 to 2+ to increased values of 3 to 4+ (as might be expected from previous test exposure). Delayed hypersensitivity test results were positive in cases 1, 2, and 4, and in case 2, delayed hypersensitivity skin test findings previously positive to *Candida*, *Trichophyton*, and streptokinase-streptodornase became negative during treatment. A response to purified protein derivative was now present.

T- and B-cell studies (in the laboratory of Dr. Roy Ritts) were done in three patients (Table I). An increase in T cells correlated with therapy in all three, and B cells correspondingly diminished.

Clinical laboratory results

The hemogram, automated blood chemistries, thyroxine determination, and serologic tests for antinuclear and rheumatoid factors yielded negative or normal results. The erythrocyte sedimentation rate was normal in three patients. The serum protein electrophoresis value was normal in all patients. The immunoglobulins were normal in three patients and slightly changed in case 3. A small amount of polyclonal cryoglobulin was found in case 3, in which the sedimentation rate was increased. The reduction of the sedimentation rate in case 3 with treatment is interesting. Values for total hemolytic complement in three patients and for C3 and C4 in one patient were normal.

Histology and immunofluorescence

Histologic findings in all four cases were consistent with prurigo nodularis. Direct immunofluorescence of biopsy specimens of lesions in each case were tested to IgG, IgM, IgA, C3, and fibrin. Seen were clumped IgM cytoid bodies in cases 2 and 4 and linear fibrin and granular IgM at the basement membrane in case 2. These reactions were interpreted as nonspecific inflammation.

DISCUSSION

Our preliminary experience with four patients in a 4-year period has confirmed the results in the literature on the treatment of prurigo nodularis with thalidomide. The six cases previously reported showed resolution of pruritus in weeks and involution of nodular lesions in several months (Table II). Our cases also showed that pruritus will diminish markedly within 2 to 4 weeks. Resolution was slow in case 1 because of lower dosage and intermittent therapy. In cases 3 and 4, the patients stopped treatment after resolution of clinical lesions was achieved in 3 and 4 months, respectively. Both patients noted an exacerbation of pruritus occurring gradually after 2 weeks and becoming definite and intense by 3 to 4 weeks. This pruritus once again responded to treatment with thalidomide, so that the initial results were confirmed. Long-term benefit may be attained by a 6-month course of therapy. In cases 1 and 2, improvement has been maintained 3 and 2 years, respectively, after the course of treatment.

Table II. *Prurigo nodularis treated with thalidomide*

Author	Age (yr) and sex	Duration (yr)	Time to improvement		Follow-up
			Pruritus (days)	Nodules (mo.)	
Mattos, 1973 (1)	NR, M	NR	15	NR	NR
	28, F	14	21	4	NR
Sheskin, 1975 (2)	48, F	14	8	2.5	NR
	68, F	8	21	3	NR
	52, F	24	21	3	NR
Winkelmann, 1978 (3)	52, F	4	60	9	3 years; improved
Van den Broek, 1980 (4)	54, M	4	NR	3	NR
Winkelmann et al.	30, F	5	21	6	2 years; improved
	52, F	4	14	3	3 months; improved
	59, F	7	21	2	6 months; improved

NR = not reported

The treatment has produced no significant side effects and has been tolerated by the patients. One patient (case 2) with a slightly elevated transaminase value at the start of treatment tolerated medication without significant change, and 6 months after treatment the value was normal. We believe that 200 mg of thalidomide a day is an adequate dose, although higher doses were used by Mattos (1) and by Sheskin (2). It is not apparent whether lower maintenance dosage might be equally effective after an initial suppression of the process.

Our studies confirmed the frequent atopic history, clinical manifestations, and elevated IgE values associated with prurigo nodularis reported in studies by Doyle et al. (5) and by Miyachi et al. (6). Direct immunofluorescence of the skin lesions is not specific, but IgE immunofluorescence studies have not been done. Specific IgE antibodies were demonstrated by RASTs in three of our four patients and were correlated with other testing for immediate hypersensitivity (Table III). Specific IgE antibodies correlating with household pets may be related to the process or could be secondary to it. A decrease in serum IgE concentration correlated with involution of the lesions during thalidomide treatment, but normal values were not reached.

Another suggestion of change in immunoreactivity is the alteration in T and B cells with therapy in one patient (case 4). The increase in patch test reactivity and in delayed hypersensitivity skin test results in this patient could represent an active enhancement of T-cell responses. The increase in T cells in three patients during treatment correlates with these changes. The suppression of previously positive delayed hypersensitivity skin test findings in case 2 is unexplained, although at the same time a negative purified protein derivative result became positive. Thalidomide has been shown to prolong graft survival in some animal systems (7) but not in others (8). Supression of the graft-versus-host reaction was demonstrated by Field et al. (9). Depressed antibody formation in rabbits was documented by Gusdon & Cohen (10), and Sagher et al. (11) noted a decrease in IgA concentration with thalidomide treatment of leprosy. Therefore, effects of thalidomide on the immune system may occur, but other explanations are possible, and more detailed studies of cell-mediated immunity are necessary.

Thalidomide decreases the inflammatory response in erythema nodosum leprosum. The mechanism by which this is accomplished has not been studied, and it is not apparent whether the drug works at an immunologic, cellular, or mediator level. It is possible that it influences all of these. Sheskin (12) showed in a double-blind study that thalidomide was effective in erythema nodosum leprosum. A similar study now needs to be performed for thalidomide in pruritic dermatoses. Preparation of a protocol for this is under way. We believe that such a study will confirm that thalidomide is an active anti-inflammatory agent and will account for its effect on discoid lupus erythematosus and actinic prurigo, also (13). A prospective study of the immunoreactive qualities of patients with these disorders may give us a further clue about the method of action of thalidomide in these circumstances.

Table III. *Atopy in prurigo nodularis treated with thalidomide*

Case	Immediate skin tests	Radioallergo-sorbent tests	IgE, ng/ml	
			Pretreatment	Posttreatment
1	Positive	Positive	13 360	4 802
2	Positive	Positive	1 434	1 091
3	Positive	Positive	3 952	1 742
4	Negative	Negative	10	10

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