

Levamisole-induced Hypersensitivity

Lena Secher, Henrik Permin, Per Stahl Skov,
Susanne Ullman and Poul Halberg

*Department of Dermatology, Municipal Hospital,
University Clinic for Infectious Diseases, Rigshospital,
Department of Dermatology, Rigshospital, and Depart-
ment of Medicine, Division of Rheumatology, Hvidovre
Hospital, Copenhagen, Denmark*

Received February 4, 1978

Abstract. A 73-year-old woman with rheumatoid arthritis was treated with Levamisole, 150 mg per day, on 2 days a week. Her arthritis improved, but she developed a severely itching rash, and the treatment was stopped after 6 months. Penicillamine was subsequently given and tolerated without skin complications. 15 months after regular Levamisole was stopped, she was given a single dose of 150 mg which provoked fever of 40°C and rash. Thirteen punch-biopsy specimens were examined by direct immunofluorescence microscopy. During the Levamisole treatment, granular deposits of IgG and C3 were found at the dermal-epidermal junction. Subsequently, the deposits disappeared, but reappeared after Levamisole challenge. The patient's leukocytes were exposed in vitro to Levamisole, and 36% of the total histamine content in the basophils was released. Our results provide further evidence that Levamisole can cause type-I as well as type-III hypersensitivity.

Key words: Levamisole; Immunofluorescence; Type-I hypersensitivity; Type-III hypersensitivity; Rheumatoid arthritis

Levamisole was first introduced as an anthelmintic, but since the drug is now known to possess anti-anergic properties, and the ability to normalize defective macrophage and microphage function, it has recently been used in the treatment of diseases in which abnormal T-cell, macrophage and granulocyte function is regularly found, in particular recurrent herpes simplex, rheumatoid arthritis (4, 12) and malignant neoplasms (6). Early observations indicated that Levamisole was well tolerated by most patients (6), but lately serious side effects have appeared, including granulocytopenia which is usually transient, but which has proved fatal in a few cases (10). Some patients develop nausea, loss of taste, loss of weight, and excitability. Skin eruptions have also been reported (11).

This is a report on a patient with rheumatoid arthritis who developed a skin eruption during treatment with Levamisole, and in whom deposits of immunoglobulin and complement components were demonstrated at the dermal-epidermal junction. Evidence of an allergic reaction to Levamisole was also found.

CASE REPORT

The patient is a 73-year-old woman with a sero-positive, erosive, nodular, deforming and very active rheumatoid arthritis of 7 years' duration. She also had xerostomia and chronic sialoadenitis as demonstrated by lip biopsy. In 1972, after gold salt therapy, she went into remission. Towards the end of 1974 she experienced a recurrence of her arthritis, and was again given gold salts. In the summer of 1975 this treatment was discontinued because of transient proteinuria and a rash. In July 1975 she was started on Levamisole, 150 mg a day, 2 days a week. The arthritis improved, and she became sero-negative. In October 1975 she developed a reddish, infiltrated, scaling and itchy skin eruption all over the body and extremities. Clinically, mycosis fungoides was suspected, but this was not confirmed histologically. Levamisole was discontinued in February 1976, and in less than 2 weeks the lesions had healed completely, leaving hyperpigmented areas. Subsequently the patient was started on Penicillamine (dimethylcysteine) 600 mg daily, which was given for more than a year without skin complications. However, her condition deteriorated, and in June 1977 Penicillamine was stopped. Once again treatment with Levamisole was attempted at a dosage of 150 mg for one day. The same evening the patient became feverish (40 °C) and during the night she developed a generalized itchy erythema. Levamisole was discontinued, and within 24 hours all symptoms disappeared. Since this episode the patient has had no skin problems.

LABORATORY RESULTS

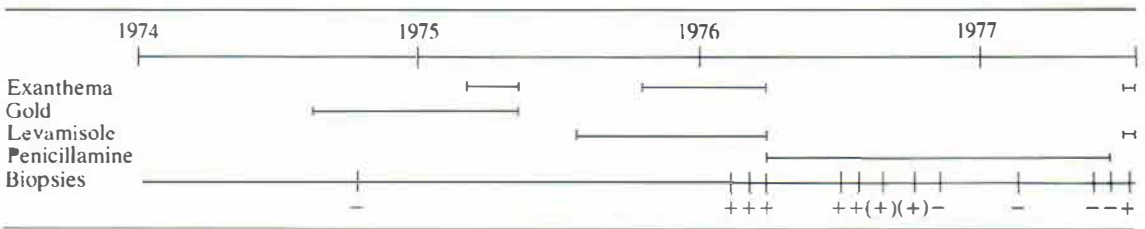
Antinuclear antibodies were demonstrated by the immunofluorescence technique (IgG, non-organ specific in a titre of 1:32, non complement fixing). Several LE-cell tests were negative, and anti-DNA antibodies were not found. The Rose-Waller sheep cell agglutination was 80 and latex fixation slide test was 32. The serum contained no immune complexes. In June 1977 the white blood cell count was $5.2 \times 10^9/\text{ml}$: lymphocytes 25%, granulocytes 71%, eosinophils 1%, monocytes 4%, and basophils $33 \times 10^9/\text{ml}$. IgG, IgA, IgM, IgD and IgE in serum were all normal. The urine was normal.

SPECIAL INVESTIGATIONS

Since November 1974 a total of 13 punch biopsies have been examined by immunofluorescence microscopy. The results are shown in Table I, which also shows the anti-rheumatic treatment and the periods of skin eruptions. The

Table 1. *Periods of anti-rheumatic treatment and exanthema. Results of immunofluorescence microscopy*

+ = granular deposits at the dermal-epidermal junction, positive for IgG and C3. - = no deposits at the dermal-epidermal junction. (+) = slight deposits



first biopsy, taken during gold therapy, showed no deposits. The biopsies examined during treatment with Levamisole revealed deposits consisting of a well marked, granular line at the dermal-epidermal junction, positive for IgG and complement C3. The changes were similar in lesional and clinically normal skin. Following discontinuation of Levamisole the deposits decreased in intensity, and after September 1976 they could no longer be demonstrated. The day after Levamisole treatment was resumed in June 1977, the deposits re-appeared at the dermal-epidermal junction. This time, the changes were most distinct in lesional skin, but also present in normal skin. No circulating basement membrane antibodies suggestive of pemphigoid were found.

The patient's basophils were investigated for liberation of histamine on in vitro challenge with various antigens including Levamisole. The investigations were carried out immediately after the last dose of Levamisole was given, and they were repeated after 2 months. The results are given in Table II. The technique has been described previously (9).

Counting of T and B lymphocytes gave the following results:

June 1977: T lymphocytes 88%, B lymphocytes 8%;

August 1977: T lymphocytes 63%, B lymphocytes 13%.

The patient was prick-tested using various dilutions of Levamisole: histamine test was used for reference. The results were as follows: Histamine: 4 mm and 6 mm. Levamisole 10 µg/ml: no reaction, 100 µg/ml: 2 mm, 500 µg/ml: 4 mm. Levamisole powder: 5 mm. Three controls showed no reaction.

DISCUSSION

Deposits at the dermal-epidermal junction of the type described in this case are seen in biopsy material from patients with immune complex disease, for instance in lesional and clinically normal skin from patients with SLE (1) and anaphylactoid purpura (13), and in the glomeruli of the kidney's in the same diseases.

Fluorescence microscopy examination of skin biopsies from patients with rheumatoid arthritis varies considerably in different investigations. Some authors frequently find deposits at the dermal-epidermal junction (3), while others fail to find any (7). The explanation might be that the deposits are caused by the anti-rheumatic treatment rather than the disease itself. Both gold salts and Penicillamine may cause the development of glomerulonephritis with deposits of immunoglobulins and complement components (presumably immune complexes) in the glomeruli (5). Immune complexes have also been demonstrated in the serum of patients treated with Levamisole (8). In the present case, serial skin biopsies revealed a very close correlation between appearance of the deposits and treatment with Levamisole. It is difficult to rule out completely any

Table II. *Basophil histamine release caused by Levamisole, DNA, RNA, Histone, Penicillamine (DMC) and Sodium aurothiomalate (SAT)*

Percentage of the total content of histamine. 1: investigation one day after the Levamisole challenge. 2: investigation 2 months after the Levamisole challenge

Antigen	Levamisole µg/ml						DNA	RNA	Histone	DMC	SAT
	100	10	1	0.1	0.01	0.001					
1	28	36	25	18	10	0	<10	<10	11	15	0
2	10	4	3	0	0	0	<10	<10	<10	13	0
5 controls	≤15	<15	<10	<10	<10	<10	<10	<10	<10	≤15	<10

effect of the gold treatment on the deposits first demonstrated, but there is no reason to suspect any relation to the treatment with Penicillamine.

The deposits at the dermal-epidermal junction might be evidence of an iatrogenic immune-complex disease, i.e. a type-III reaction. The last episode of fever and rash, induced by Levamisole, developed in a very short time, and the findings of histamine liberation on challenge of the patient's basophils as well as the positive prick tests indicate a type-I reaction as an additional pathogenic factor. Evidence of reaginic hypersensitivity to Levamisole as well as to gold salts has previously been found by other techniques (2, 14).

REFERENCES

1. Baart de la Faille-Kuyper, E. H.: Lupus erythematosus. An immunohistochemical and clinical study of 485 patients. Ph.Md. Thesis, University of Utrecht, 1969.
2. Davis, P., Munro, J., Hobbs, J. R. & Hughes, G. H. V.: Immunological studies on the mechanism of gold hypersensitivity. *Br Med J* 676-678, 1973.
3. Donde, R., Permin, H., Juhl, F., Wiik, A., Hansen, N. E. & Andersen, R. B.: Immune deposits in the dermo-epidermal junction in rheumatoid arthritis. *Scand J Rheumatol* 6: 57-61, 1977.
4. Huskisson, E. C., Dieppe, P. A., Scott, J., Trapnell, J., Balme, H. W. & Willoughby, D. A.: Immunostimulant therapy with Levamisole for rheumatoid arthritis. *Lancet* *ii*: 393-395, 1976.
5. Jaffe, I. A., Treser, G., Suzuki, Y. & Ehrenreich, T.: Nephropathy induced by D-Penicillamine. *Ann Intern Med* 69: 549-556, 1968.
6. Levamisole. Technical review. Janssen Pharmaceuticals, 1976.
7. Moer, M. van de & Cats, A.: Immunofluorescence of the skin in patients with rheumatoid arthritis. *Dermatologica* 134: 351-55, 1967.
8. Parkinson, D. R., Cano, P. O., Jerry, L. M., Capek, A., Shibata, H. R., Mansell, P. W., Lewis, M. G. & Marquis, G.: Complications of cancer immunotherapy with Levamisole. *Lancet* *ii*: 1129, 1977.
9. Permin, H., Stahl Skov, P., Norn, S. & Juhl, F.: Basophil histamine release by RNA, DNA and aggregated IgG examined in rheumatoid arthritis and systemic lupus erythematosus. *Allergy* 33: 15-22, 1978.
10. Ruuskanen, O., Remes, M., Mäkelä, A. L., Isomäki, H. & Toivanen, A.: Levamisole and agranulocytosis. *Lancet* *ii*: 958, 1976.
11. Symoens, I. & Rosenthal, M.: Levamisole in the modulation of the immune response: The current experimental and clinical state. *Reticuloendothel Soc* 21: 175, 1977.
12. Szpilman, H., Luft, S., Ghuska-Urban, D., Fischer, W. & Placheka, M.: Levamisole and cell mediated and serum immunoglobulins in rheumatoid arthritis. *Lancet* *ii*: 208-209, 1976.
13. Ullman, S., Halberg, P., Nielsen, B., Jørgensen, F. & Balslöv, J. T.: Deposits of immunoglobulins and complement in the dermo-epidermal junction of patients with anaphylactoid purpura. *Acta Dermatovener (Stockholm)* 55: 359-362, 1975.
14. Yust, I., Vardinon, N., Fiersteter, E. & Avramov, L. A.: Levamisole induced allergy. *Lancet* *i*: 457, 1977.

Acne-like Eruptions Induced by PUVA-Treatment

Eivind B. Nielsen and
Jens Thormann

*Department of Dermatology, Marselisborg Hospital,
University of Aarhus, Aarhus, Denmark*

Received December 27, 1977

Abstract. Photochemotherapy with psoralen and long-wave ultraviolet light, so-called PUVA-treatment, is currently being evaluated in many dermatologic departments. Side effects such as nausea, pruritus and erythema are well known. Recently the development of acneiform eruptions was reported in a British patient treated with PUVA (3). We found that 4 out of 80 patients treated in our clinic with 8-methoxy-psoralen according to the usual weight schedule (6) and long-wave ultraviolet irradiation developed perioral dermatitis, in 2 cases, together with acneiform eruptions localised to the forehead.

Key words: Acne; Perioral dermatitis; PUVA treatment; Rosacea

CASE REPORT

Case I

This 35-year-old female with vitiligo was treated with PUVA for 4 months before she developed small red papules and pruritus on the distal half of the face. No pustules were seen. PUVA treatment was discontinued but the skin changes persisted. After 3 weeks, therefore, treatment with tetracycline (1 g orally, daily) was instituted 2 weeks later the dermatitis cleared.

Case II

The second patient, a 26-year-old female with extensive psoriasis, was also treated with PUVA. After 2 months she developed an itching and burning rash characterised by scaling, erythema and small papules in the perioral region. UVA irradiation to the face was prevented by shielding and the rash then disappeared gradually without any other counter-measure.