The red man syndrome

Exfoliative dermatitis of unknown etiology: A description and follow-up of 38 patients

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Thirty-eight patients with erythroderma of unknown etiology were diagnosed over a 15-year period, and represented 19% of all patients admitted to our department for erythroderma. The male:female ratio was 6.6:1, and the median disease duration was 2 years (range 1 to 23 years). Keratoderma of palms and/or soles was seen in 79%. Laboratory findings were normal, except for an increased IgE level in 69% of the patients studied. Lymph node histology showed dermatopathic lymphadenopathy. Bone marrow investigation results were normal in 48%, or showed eosinophilia (32%) or hyperplasia (20%). Initial skin biopsies showed nonspecific histology in most patients, but later biopsies revealed pleomorphic infiltration. During the observation period four patients progressed to mycosis fungoides and another nine patients were suspected of having mycosis. None developed Sézary's syndrome. Only one third of the patients went into complete remission; half of them died during the observation period. Patients with erythroderma of unknown etiology are predominantly men and seem to belong to a certain subgroup—herein called the red man syndrome. (J AM ACAD DERMATOL 1988;18:1307-12.)

Erythroderma or exfoliative dermatitis is a relatively rare, severely disabling skin disorder. It is seen in most patients as an exacerbation of a preexisting dermatologic disease. However, it can indicate an internal malignant disease or later development of a malignant disorder, most often mycosis fungoides.

We undertook this study to delineate a particular group of patients with exfoliative dermatitis, herein called the red man syndrome. It is diagnosed in patients in whom no underlying cause can be established for the exfoliative dermatitis. Patients with exfoliative dermatitis have few abnormal laboratory findings, a nonspecific skin histology, and no malignant lymph node or bone marrow changes. Most of the patients are men, who continue to have their disease for years. A significant clinical finding is keratoderma of palms and soles. We describe 38 patients with the red man syndrome seen over a period of 15 years and follow the outcome of their disease.

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PATIENTS AND METHODS

All patients in this study were inpatients in our department between 1972 and the end of 1986, a 15-year period. The department serves a population of about 1 million people. We have included every patient with a diagnosis upon discharge of exfoliative dermatitis with or without a concomitant skin disease. Information was obtained from the records of each patient and included clinical findings, laboratory test results, and histologic investigations. All skin biopsy specimens have been

Table I. Age, sex distribution, and sex ratio of 204 patients admitted for erythroderma, 1972-1986

Cause of erythroderma	Age (yr) (range)	Men		Women		Total		Male:female ratio
		No.	%	No.	%	No.	%	
Psoriasis	54 (1-91)	38	73	14	27	52	25	2.7
Atopic dermatitis	32 (1-64)	15	58	11	42	26	13	1.4
Miscellaneous	64 (1-95)	55	63	33	37	88	43	1.7
Red man syndrome	69 (34-87)	33	87	5	13	38	19	6.6

Table II. Causes of exfoliative dermatitis in the miscellaneous group

Diagnosis	No. of patients	% of miscellaneous group	% of total group
Drug allergy	28	32	16
Contact dermatitis	18	21	9
Seborrheic dermatitis	16	18	8
Internal malignancy*	10	11	5
Other†	16	18	8

*Internal malignancy included malignant melanoma (one), pulmonary cancer (three), lymphatic leukemia (two), ovarian cancer (one), rectal cancer (one), mammary cancer (one), and prostate cancer (one).
†This group includes patients with ichthyosis, polymorphous light eruption, vitamin deficiency, collagenosis, hepatitis, parapsoriasis en plaque, pityriasis rubra pilaris, dermatophytosis, prurigo, and scabies.

evaluated by the same person (H. S.) throughout the study.

We have divided the patients into four groups: patients whose exfoliative dermatitis was an exacerbation of psoriasis or of atopic dermatitis; patients whose exfoliative dermatitis was judged to be a consequence of drug allergy, contact allergy, seborrheic dermatitis, or some other well-defined reason (the miscellaneous group); and patients without an evident cause for their exfoliative dermatis (the red man syndrome group).

All patients with red man syndrome were traced. Death certificates were obtained from deceased patients and the remaining were seen in our clinic or contacted through telephone or questionnaire.

Table III. Various clinical and laboratory parameters in the group of patients with miscellaneous disorders as background for erythroderma and patients belonging to the group with red man syndrome

Parameter	Red man syndrome		Miscellaneous	
	No.	%	No.	%
Keratoses of palms and soles				
Yes	30	79	38*	43
No	8	21	50	57
Disease duration				
Median	2 yr		1 mo	
Range	1-23 yr		¼ mo-10 yr	
IgE evaluation†				
Not done	12		70	
<150 IU	8	31	7	39
>150 IU	18	69	11	61
>1000 IU	7		3	

*These patients had "eczematous changes" of their hands. Their diagnoses were drug allergy, contact eczema, or seborrheic eczema (see Table II).
†IgE levels: <150 IU = within normal limits; >150 IU = higher than normal; >1000 IU = highly increased (data included among those having higher-than-normal IgE levels).

RESULTS

A total of 204 patients were admitted for exfoliative dermatitis from 1972 through 1986, averaging 13.6 patients per year. Admissions for exfoliative dermatitis were evenly distributed during the observation period; atopic dermatitis has

Table IV. The previous dermatologic disorder in patients with red man syndrome or miscellaneous erythroderma

Diagnosis	Red man syndrome		Miscellaneous	
	No.	%	No.	%
Eczema	13	34	33	38
Prurigo	5	13	2	2
Ichthyosis	4	11	6	7
Seborrheic eczema	3	8	5	6
Psoriasis	3	8	3	3
Drug allergy	3	8	2	2
Other*	2	5	2	2
None	5	13	35	40

*Photodermatitis, scabies, and alcoholism.

Table V. The initial and last histologic skin examination results from patients in the red man syndrome group

Histologic picture	Initial biopsy	Last biopsy
Nonspecific	26	17
Psoriasiform*	7	5
Pleomorphic†	5	8
Mycosis fungoides	0	8
Total	38	38

*Elongated dermal papillae with some thinning of overlying epidermis. Scanty pleomorphic lymphocytes.
†Dermal accumulation of many pleomorphic lymphocytes, in some areas exocytosis, but no Pautrier's microabscesses.

shown a trend to increase during recent years.

Table I describes the classification, age, sex distribution, and sex ratio of the patients. Patients with red man syndrome formed 19% of all patients with exfoliative dermatitis, whereas miscellaneous disorders were responsible for 43% of cases of exfoliative dermatitis. The causes for exfoliative dermatitis in these patients are listed in Table II. Of the miscellaneous group, 32% had exfoliative dermatitis caused by drug allergy, 18% caused by seborrheic dermatitis, and 15% caused by allergic contact dermatitis. Patients with exfoliative dermatitis caused by internal cancer formed 11% of the miscellaneous group and 5% of all patients with exfoliative dermatitis. We observed only one patient with exfoliative dermatitis caused by dermatophytosis. Skin cultures were not regularly performed in our patients, occurring only upon clinical suspicion of infection.

We decided to evaluate patients belonging to the red man syndrome and miscellaneous groups (Table II). Patients with exfoliative dermatitis from psoriasis or atopic dermatitis are relatively easy to diagnose, and it is among the remaining patients with exfoliative dermatitis that diagnostic problems may occur. Three observations seem to differ significantly between the two groups. The sex ratio in the red man syndrome group was 6.6:1 (men:women), compared with 1.7:1 in the miscellaneous group (Table I). Second, 79% of all patients with red man syndrome had keratoderma of hands and/or feet (Table III). All men except for five had keratoderma. Third, the median disease duration was 2 years in the red man syndrome group, compared with 1 month in the miscellaneous group, in which only four patients had their exfoliative dermatitis for more than 1 year. Laboratory investigations revealed that patients with red man syndrome tended to have increased IgE levels (Table III).

Both the red man syndrome and miscellaneous groups had a history of previous skin disease whose median length of time was 6 years and 3 years, respectively (Table IV). Eczema was the most common disease, and usually occurred in the legs. Fourteen of 38 patients with red man syndrome (37%) and 33 of 88 patients with miscellaneous causes (37%) were known to have had a previous positive patch test. The allergens were metals, cosmetics, thiram mix, or topical medication. The contact allergy in patients with red man syndrome was not considered of relevance for the erythroderma; their history of eczema occurred years before their present symptoms, and although they were not exposed to the allergens they continued to have their present exfoliative dermatitis. There was no difference between the two groups in previous atopic disorders of medication.

The skin histology was nonspecific in 26 of 38 biopsy specimens at the initial investigation (Table

Table VI. Systemic treatment for patients in the red man syndrome or miscellaneous groups

Treatment	Red man syndrome		Miscellaneous	
	No.	%	No.	%
Prednisone	21	55	32	36
Topical nitrogen mustard	17	45	3	3
Chemotherapy*	11	29	0	
Psoralens plus ultraviolet A	10	26	4	5

Some patients were given more than one kind of systemic therapy. These were patients who were later found to progress to mycosis fungoides (see "Chemotherapy" for red man syndrome group).
*Prednisone, cyclophosphamide, bleomycin, and etretinate (since (1980).

Table VII. The course of exfoliative dermatitis in patients with red man syndrome

Course	Total No.	Living	Dead
Complete remission	12	11	1
Partial remission	16	3	13
No change	3	1	2
Worsening	2	0	2
Nonevaluable	5	4	1

V). The number of biopsies ranged from 1 to 17 (median = 5). Sixteen patients (42%) had pleomorphic changes in their last biopsy specimen. Four patients (11%) had progressed to mycosis fungoides, and another nine (24%) were suspected thereof; none progressed to Sézary's syndrome. Among the miscellaneous group 28 of 39 had nonspecific skin histology, and later biopsies showed pleomorphic changes in only four patients (10%). Twenty-nine of 38 patients with red man syndrome had enlarged lymph nodes; 23 had a lymph node biopsy, with dermatopathic lymphadenopathy in 20, reactive hyperplasia in two, and a possible lymphoma in one. Twenty-five patients with red man syndrome had a bone marrow investigation; 12 (48%) were normal, eight (32%) showed eosinophilia, and five (20%) were hyperplastic. Only seven of the patients in the miscellaneous group underwent bone marrow aspiration; four

Table VIII. Final diagnosis in the red man syndrome group

Final diagnosis	No. of patients
Erythroderma	18
Mycosis fungoides observatio	9
Mycosis fungoides	4
Reticulosis	2
Poikiloderma	1
Other*	4

*Psoriasis observatio, seborrheic dermatitis observatio, drug allergy observatio, and chronic lymphatic leukemia observatio. The suffix *observatio* is used in patients who clinically had mycosis fungoides, but whose histologic examinations showed no signs of Pautrier's microabscesses in the epidermis.

were normal and the remaining showed hyperplasia, chronic lymphoid leukemia, or myelomatosis.

A pronounced symptom in exfoliative dermatitis is severe itching. All patients were treated with topical steroids, which was sufficient therapy in most of the miscellaneous group. The subjective and objective symptoms in patients with red man syndrome were very resistant to therapy. Table VI shows that intensive systemic therapy is needed in most cases. Topical nitrogen mustard is effective in relieving itching.

Our red man syndrome group was followed for a median of 30 months; 19 of 38 have died. The cause of death in most patients was respiratory tract infections or cardiac disease. None died primarily because of their skin disease, although it must have predisposed them to respiratory infections. The course of exfoliative dermatitis in the patients with red man syndrome and their final clinical diagnosis at the last observation date are listed in Tables VII and VIII, respectively. The younger patients tended to have the best chance for complete remission of their exfoliative dermatitis. Patients who developed suspected or confirmed mycosis were observed for a median of 48 months.

DISCUSSION

Exfoliative dermatitis has been discussed in the dermatologic literature for decades.[1-9] Early classification of exfoliative dermatitis was accomplished by Baxter,[4] who defined a primary or id-

Table IX. Literature review of various causes for erythroderma

Etiology	Relative incidence (%)							
	Ref. 2	Ref. 3	Ref. 5	Ref. 6	Ref. 7	Ref. 8	Ref. 9	Present
Dermatosis	48	25	32	55	42	33	30	38
Drug allergy and miscellaneous disorders	16	42	14	?	22	25	34	38
Malignancy	10	21	8	15	4	0	20	5
Undetermined	26	12	46	30	32	23	16 (?)	19

The table does not include all mentioned causes of erythroderma. Therefore, the total percentage does not always equal 100%.

iopathic form and a secondary form in which preexisting dermatosis was present. Montgomery[1] defined malignant erythroderma as "a generalized or universal erythrodermatous phase of any of the types of lymphoblastoma, in which the clinical picture is not diagnostic . . .." Later studies have all shown that a minor group of patients with exfoliative dermatitis have a disease that cannot be determined[1-9] (Table IX). It is rather remarkable that patients with exfoliative dermatitis of unknown causes form between 16% and 46% of all patients with erythroderma. Men predominate over women in all studies.

Our results suggest that a man with exfoliative dermatitis, keratoderma of palms and soles, nonspecific skin histology or some pleomorphic infiltration, and exfoliative dermatitis extending over 1 month is very likely to have what we call the red man syndrome. These patients may clinically be considered to have pré-Sézary syndrome, as suggested by Winkelman et al,[10] who followed 18 patients for a period of 5 years. However, none of their patients developed Sézary's syndrome, and our results support their observation. Thus we found 13 of 38 patients (34%) developed mycosis fungoides or were suspected of having mycosis; furthermore, two cases were classified as reticulosis and one was termed poikiloderma (Table VII).

The pathophysiology of patients with exfoliative dermatitis is largely unknown. Rook and Champion[11] looked for autologous antibodies toward the skin in 67 patients with exfoliative dermatitis, but found evidence for this in only four patients. It has been suggested by Heng et al[12] that *Staphylococcus aureus* infection may be responsible for a chronic immune stimulation leading to erythroderma. Their hypothesis is supported by the efficacy of antibiotic therapy in 11 patients, in whom antibiotic therapy for 2 to 8 weeks cleared the erythroderma. However, most patients had an underlying dermatologic disorder such as atopy or psoriasis, and therefore do not fall under the red man syndrome classification. While partial remission of the exfoliative dermatitis was observed in conjunction with decreased staphylococcal colonization of the skin, complete remission was observed only after the culture results became negative. We have not performed skin cultures in our patients with red man syndrome, nor have we treated them with antibiotics for longer periods of time.

The treatment of red man syndrome is difficult. The disease duration in our patients was about 2 years. Some patients may be very resistant to therapy, even chemotherapy. We observed that the disease in most patients can be controlled by topical and systemic steroids; severe itching can be relieved by topical nitrogen mustard. "Cure," however, is observed only in 32% (12 of 38 patients), and half of our patients died with symptoms of exfoliative dermatitis.

The present investigation seems to indicate that patients with red man syndrome belong to a subgroup of patients with exfoliative dermatitis: men with keratoderma of palms and soles and a long-lasting disease that is difficult to treat. The patients are generally older than other patients with exfoliative dermatitis. There is no obvious cause for the exfoliative dermatitis. One could speculate that red man syndrome involves a chronic immune stimulation through a previous eczematous con-

dition or a skin infection. We cannot evaluate the eventual significance of *S. aureus* as a possible stimulating antigen, as suggested by Heng et al.[12] Another possibility is that patients with red man syndrome are in the process of a slow, malignant transformation. The observed imbalances in their immune system, such as dermatopathic lymphadenopathy, increased IgE levels, and eosinophilia of their bone marrow, are also observed in patients who later develop malignant lymphoma. This hypothesis is supported by our finding of the development of mycosis fungoides as judged by histologic criteria.

We believe that it is helpful for the clinician to delineate this particular group of patients with exfoliative dermatitis from a diagnostic, therapeutic, and prognostic point of view.

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