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Letter to the Editor

The relationship between the development of erythroderma in patients with atopic dermatitis and the avoidance of anti-inflammatory topical drugs

Dear Editor,

Erythroderma, also known as exfoliative dermatitis, is the term used to describe any inflammatory skin conditions that affect more than 90% of the body's surface.¹ It often develops with a sudden onset, and with a rapidly extending erythema, e.g. within 48 h.¹ Atopic dermatitis (AD) is a common skin disorder, characterized by itch and repetitive improvement and aggravation. It may be well controlled by standard treatment with anti-inflammatory medications, such as topical corticosteroids (TCS) and topical calcineurin inhibitors (TCI), and possibly systemic medications, such as dupilumab, cyclosporine, or oral corticosteroids.^{2–4} However, it rarely develops into erythroderma, which affects not only the skin, but also systemic organs, leading to a general deterioration of health with consequences such as severe infection and hypoproteinaemia. Inadequate treatments and home remedies used for patients with AD have been suggested as factors associated with the development of erythroderma.⁵ However, an apparent relationship between the development of erythroderma and preceding treatments of AD is unclear. Erythroderma may develop in patients with AD despite being treated at medical institutions. Moreover, there is no clear indication for additional or modifying treatments for such patients. In this study, we retrospectively investigated the clinical backgrounds and course of subsequent treatments of AD for patients, who developed erythroderma and visited the Department of Dermatology at the allergy centre in Hiroshima University Hospital.

All clinical records of 478 new AD patients who visited the Hospital for the first time from January 2014 to January 2019 were reviewed retrospectively. It included 34 patients with erythroderma, defined as diffuse erythema with overlying scales covering more than 90% of the body's surface. Backgrounds that may have influenced the development of erythroderma of all patients with erythrodermic AD and those of 34 patients randomly selected from 444 patients with non-erythrodermic AD are shown in [Supplementary Table 1](#). Among them, the use of "TCS" and "no anti-inflammatory drug according to the patient's will" were found to be significantly associated with the non-erythrodermic AD group and the erythrodermic group, respectively ([Supplementary Table 1](#)). This result suggests the association of the avoidance of topical anti-inflammatory drugs and

the development of erythroderma. Details of the treatments of 34 patients with erythroderma before and after the first visit to the Hospital are shown in [Table 1](#). All 13 (38%) patients who used "no anti-inflammatory drugs" for the treatment expressed TCS phobia and intentionally avoided treatments with topical or systemic anti-inflammatory drugs, before the onset of erythroderma (Group A in [Fig. 1](#)). Nine of them developed erythroderma within 3 months after stopping the use of anti-inflammatory medications ([Table 1](#)). The other 21 patients used TCS and/or TCI before the onset of erythroderma (Group B in [Fig. 1](#)). On the other hand, of the 444 patients without erythroderma, 17 (3.8%) avoided treatments with anti-inflammatory drugs ([Fig. 1](#)). We confirmed the relationship between the avoidance of treatments and the development of erythroderma by the test for independence (χ^2 test, $P < 0.001$, Supplementary Methods and Results). As to why these patients avoided using anti-inflammatory drugs is another point of discussion. In Group A, TCS use before the cessation of treatment has been confirmed in 12 cases ([Table 1](#)). [Supplementary Table 2](#) presents the reasons argued by the patients for TCS avoidance. Most of them are related to vague anxiety about side effects of TCS. All patients with erythroderma received education about the correct use of TCS and the potential side effects. After that, all patients in Group A accepted TCS treatment. Moreover, all patients with erythroderma, including those who had noted that TCS were ineffective before the education, achieved satisfactory control of dermatitis with proper use of steroids ([Table 1](#)). Previous reports have also demonstrated the effectiveness of patient education in countering steroid phobia.⁶ TCS phobia may be caused by a patient's inadequate understanding about TCS and their experiences of treatment failure due to incorrect use of TCS.

A retrospective investigation of the treatment of patients in Group B, who were using TCS at the onset of erythroderma, also revealed that the treatment of AD before or at the onset of erythroderma may have been inappropriate. In severe cases of AD, which have a potential of developing erythroderma, daily use of sufficient amount of TCS is necessary. However, only 3 out of 21 patients in this group used TCS daily. The treatments at the onset of erythroderma were unknown in 5 patients, and undertreated (e.g. partial external use only during exacerbations or insufficient application of TCS) in the other 13 patients ([Table 1](#)). After receiving education regarding the appropriate treatment with TCS according to the guidelines, all patients with erythroderma became controlled. Moreover, most of them are currently keeping

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Table 1
Characteristics of patients with AD who developed erythroderma.

	Group A (N = 13)	Group B (N = 21)	Total (N = 34)
Mean age (SD)	29.1 (13.5)	38.2 (12.2)	34.7 (13.3)
Female: Male	8:5	6:15	14:20
Mean EASI score (SD), number of surveyed patients [†]			
First visit	41.9 (12.9), 13	43.3 (8.7), 21	44.1 (8.3), 34
One month later from the first visit	20.3 (7.8), 12	28.0 (7.7), 21	25.2 (8.5), 33
One year later from the first visit	5.6 (2.8), 8	10.9 (5.1), 5	7.6 (4.5), 13
Mean blood test data at the first visit (SD), number of surveyed patients [‡]			
WBC, 10 ³ cell/ μ l	8.6 (3.1), 13	8.8 (2.1), 20	8.9 (2.0), 33
Eo, 10 ³ cell/ μ l	4.6 (7.5), 13	1.3 (8.2), 20	3.0 (5.3), 33
LDH, IU/l	445 (114), 11	390 (119), 19	414 (116), 30
CRP, mg/dl	1.1 (2.5), 10	0.8 (1.1), 8	1.0 (2.0), 18
IgE, 10 ³ IU/mL	15.7 (17.2), 13	23.7 (34.8), 20	20.4 (29.2), 33
TARC, 10 ³ pg/mL	18.6 (10.3), 13	12.7 (10.0), 21	15.0 (10.5), 33
Periods from the patient's cessation of TCS and TCI to the onset of erythroderma, no (%)			
0–1 month	4 (30.8)		
1–3 months	5 (38.5)		
3–12 months	2 (15.4)		
More than 1 year	2 (15.4)		
Usage of TCS/TCI before the patient's cessation, no (%)			
Partial use only when exacerbated	7 (53.8)		
A small amount of TCS occasionally	1 (7.7)		
Unknown	4 (30.8)		
No experience	1 (7.7)		
Usage of TCS/TCI at the onset of erythroderma, no (%)			
Daily use		3 (14.3)	
Partial use only when exacerbated		12 (57.1)	
A small amount of TCS occasionally		1 (4.8)	
Unknown		5 (23.8)	
Treatment started at the first visit, no (%)			
Daily use of TCS (high potency)	12 (92.3)	19 (90.5)	31 (91.2)
Daily use of TCS (medium potency)	1 (7.7)	1 (4.8)	2 (5.9)
Treatment 1 year after the first visit, no (%)			
Usage of TCS/TCI as remission maintenance therapy; proactive therapy			
Daily use	1 (7.7)	3 (14.3)	4 (11.8)
Every other day	0 (0)	3 (14.3)	3 (8.8)
Twice a week	2 (15.4)	3 (14.3)	5 (14.7)
Once a week	8 (61.5)	7 (33.3)	15 (44.1)
Systemic therapy combined with/without topical therapy [§]			
Dupilumab	0 (0)	2 (9.5)	2 (5.9)
Cyclosporine	0 (0)	1 (4.8)	1 (2.9)
Unidentified	2 (15.4)	3 (14.3)	5 (14.7)
Follow-up period less than 1 year	1 (7.7)	0 (0)	1 (2.9)

Group A: Patients who avoided use of TCS and TCI before the onset of erythroderma. Group B: Patients who continued treatment with TCS and/or TCI before the onset of erythroderma.

SD, standard deviation; WBC, white blood cell; Eo, eosinophil granulocytes; LDH, lactate dehydrogenase; CRP, C-reactive protein; IgE, immunoglobulin E; TARC, thymus and activation-regulated chemokine; EASI, Eczema Area and Severity Index; TCS, topical corticosteroids; TCI, topical calcineurin inhibitors.

[†] Mean EASI scores were calculated only for patients whose EASI score could be extracted from the medical record.

[‡] Mean blood test data were calculated only for patients whose data could be extracted from the medical records.

[§] All patients who received systemic therapy 1 year after the first visit had poor adherence to topical treatment.

their skin in good condition by proactive treatment using TCS or TCI. Only three patients were treated with dupilumab or cyclosporine one year after the first visit because of poor adherence to topical treatments (Table 1). These results suggest that physicians should consider not only refractoriness to the drugs, but also consider whether the drugs have been used appropriately, when patients develop erythroderma during treatment with topical anti-inflammatory drugs.

This retrospective observational study had several limitations. The information about the treatment before the onset of erythroderma depended on the subjectivity of the patients and there was a selection bias because only patients who, came to the clinic specialized to the treatments of allergic diseases, were enrolled. However, this study of 34 cases has suggested a relationship between development of erythroderma and self-cessation of conventional treatment, and has shown the effectiveness of adequate

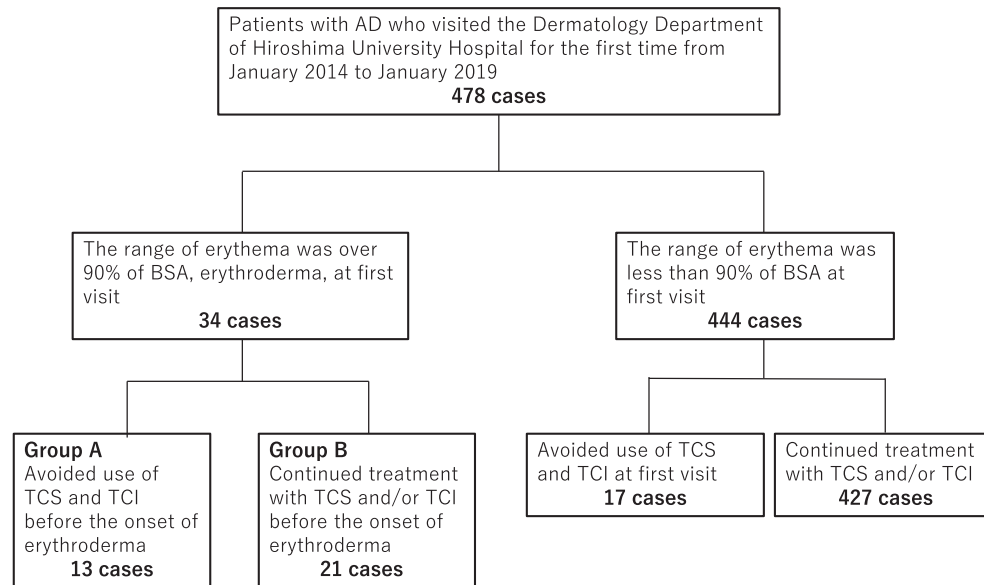


Fig. 1. Diagram of patients with AD and their treatments. A total of 487 patients visited the Dermatology department of Hiroshima University Hospital for the first time between January 2014 and January 2019. Of these patients, 34 cases suffered from erythroderma. AD, atopic dermatitis; BSA, body surface area; TCS, topical corticosteroids; TCl, topical calcineurin inhibitors.

topical treatment and therapeutic patient education for treatment of erythrodermic AD.

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This study was approved by the Ethics Committee for Epidemiological Research of Hiroshima University. The approval number is E-2056.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.alit.2020.11.009>.

Conflict of interest

AT received honorarium for lectures from Maruho, Japan; Sanofi, Japan. MH received honorarium for lectures from Taiho Pharma, Japan; Mitsubishi-Tanabe Pharma, Japan; Maruho, Japan. The rest of the authors have no conflict of interest.

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Supplementary Table 1. Backgrounds of the patients with erythrodermic AD and those with non-erythrodermic AD

	Erythrodermic AD patients (N = 34)	Non-erythrodermic AD patients* (N = 34)	Total (N = 68)	<i>p-value</i>
Occupation				
Student	6	7	13	0.762
Professional job	5	10	15	0.148
Office job	6	8	15	0.388
Service, sales job	2	0	2	0.156
Technician, engineer	0	1	1	0.321
Labour worker	2	5	7	0.238
Self employed	1	0	1	0.321
Jobless	9	3	13	0.127
Unknown	3	0	3	0.078
Pet breeding				
Dogs	2	3	5	0.648
Cats	1	0	1	0.321
None	31	31	62	1.000
Medical history, non-allergic disorders (multiple answers)				
Digestive disorders	4	7	11	0.331
Renal disease	1	2	3	0.562
Cardiovascular disorders	1	1	2	1.000
Gynecological diseases	1	3	4	0.310
None	27	22	49	0.182
Medical history, allergic disorders (multiple answers)				
Asthma	13	10	23	0.449
Allergic rhino-conjunctivitis	8	10	18	0.589
None	17	17	34	1.000
Smoking history				
Smoking	6	7	13	0.762
Habitual drinking				
Drinking	4	4	8	1.000
Aggravating factors for AD (multiple answers)				
Sweats	3	5	8	0.459
Seasonal changes	3	1	4	0.310

Stress	2	0	2	0.156
Food allergy (raw egg/milk)	4	2	6	0.400
None	24	26	50	0.589
Treatments of AD (multiple answers) §				
Systemic therapy	0	0	0	
TCS	21	33	54	0.0002†
TCI	3	4	7	0.695
No anti-inflammatory drugs according to the patient's will	13	1	14	0.0002‡

The *t-test* was performed to assume that the variances of the erythrodermic AD patients' group and the non-erythrodermic AD patients' groups were equal. Then, the probability was calculated as the *p-value* as $\text{Prob}>|t|$. Both variables “TCS” (†) and “No anti-inflammatory drug according to the patient's will” (‡) were the primary factors for the difference between the two groups. Since the probability of equal variance was almost zero about these two factors, we concluded a significant difference between these two groups.

*Thirty-four patients with non-erythrodermic AD were randomly selected from 444 AD patients without erythroderma who visited Hiroshima University Hospital for the first time from January 2014 to January 2019.

§Therapies/medications taken before the development of erythroderma for erythrodermic AD patients, and those before the first visit to Hiroshima University Hospital for non-erythrodermic AD patients.

AD, atopic dermatitis; TCS, topical corticosteroids; TCI, topical calcineurin inhibitors.

Supplementary Table 2. The reasons why the patients in Group A discontinued TCS

Age, sex	Period using TCS	EASI score at first visit	Reason for stopping TCS
10, male	5–10 years	42	I didn't want to use strong medicines too much.
13, female	10–15 years	36	I thought TCS was dangerous drug.
14, male	No history of use	36	My mother said using TCS would accumulate carcinogens.
22, female	10–15 years	60	Treatment with TCS did not improve my symptoms.
27, male	5–10 years	48	I was afraid that TCS would make my skin go wrong.
28, female	10–15 years	48	I am fed up with continuous use of TCS.
29, female	15–20 years	48	I felt that TCS was ineffective, and made my arm swollen.
30, male	5–10 years	60	Somehow the side effects were scary.
31, female	0–5 years	41	My eczema worsened when I stopped TCS.
34, female	10–15 years	36	Somehow the side effects were scary.
38, female	25–30 years	42	My eczema worsened when I stopped TCS.
42, male	20–25 years	54	I somehow stopped TCS
61, female	>30 years	48	Unidentified

TCS, topical corticosteroids.

Supplementary Methods and Results

Statistical analysis

The following tests were performed to verify an association between the avoidance of topical anti-inflammatory drugs and the erythroderma. Supplementary Table 3 described below was created based on the results shown in Figure 1. We verified how much these measured values deviated from the theoretical values. The statistical evaluation was performed by the χ^2 test.

Supplementary Table 3. Measured values.

	Treatment with anti-inflammatory drugs	Avoided use of anti-inflammatory drugs	Total
Erythroderma	21	13	34
Non-erythroderma	427	17	444
Total	448	30	478

The theoretical values were calculated using from formula (1) to (9) based on the values of each cell shown in Supplementary Table 4

Supplementary Table 4

	Treatment with anti-inflammatory drugs	Avoided use of anti-inflammatory drugs	Total
Erythroderma	a	b	X
Non-erythroderma	c	d	Y
Total	V	W	N

$$a = X \cdot V / N \quad (1)$$

$$b = X \cdot W / N \quad (2)$$

$$c = Y \cdot V / N \quad (3)$$

$$d = Y \cdot W / N \quad (4)$$

$$X=a+b \quad (5)$$

$$Y=c+d \quad (6)$$

$$V=a+c \quad (7)$$

$$W=b+d \quad (8)$$

$$N=X+Y=V+W \quad (9)$$

The results are shown in Supplementary Table 5.

Supplementary Table 5. Theoretical values.

	Treatment with anti-inflammatory drugs	Avoided use of anti-inflammatory drugs	Total
Erythroderma	32	2	34
Non-erythroderma	416	28	444
Total	448	30	478

The null hypothesis and the alternative hypothesis were set as follows.

Null hypothesis: There is no association between the difference between erythroderma patients and non-erythroderma patients and the avoidance of anti-inflammatory drugs.

Alternative hypotheses: Differences between erythroderma patients and non-erythroderma patients are associated with the avoidance of anti-inflammatory drugs.

Based on the measured and theoretical values, we calculated the value of χ^2 and found it to be 63.56. Then, we calculated the p -value based on the χ^2 value, whether the null hypothesis was correct. This resulted in a $p < 0.001$. The null hypothesis was rejected, and this response difference was not a random error.