SHORT COMMUNICATION

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Clinical and Laboratory Differences between Steroid-associated and Non-steroid-associated Rosacea: A Retrospective Study

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Excessive use of topical steroids for over 2 months is well known to cause steroid-induced rosacea, with mechanisms such as rebound vasodilation and pro- inflammatory cytokine secretion proposed as pathogenesis (1, 2). Specifically, when applied to the facial area, the thin corneal layer and high skin permeability through numerous sebaceous glands increase the risk (2, 3). It is known that the risk of adrenocortical insufficiency due to the use of topical steroids increases when they are used on areas with thin skin, such as the face, or when high-potency steroids are used for an extended period (4). While there exists descriptive research on the clinical classification and accompanying symptoms of steroid-associated rosacea based on lesion distribution, in-depth investigation into its clinical and laboratory characteristics is lacking (1, 2, 5, 6).

MATERIALS AND METHODS

We retrospectively analysed the medical records of patients diagnosed with rosacea who visited the Dermatology Department at Boramae Medical Center between September 2020 and March 2023. Following an IRB-approved protocol, we assessed steroid usage history, rosacea type, affected areas, and baseline laboratory features including serum cortisol and adrenocorticotropic hormone (ACTH) levels. The study participants were categorized based on their previous history of steroid use. Those with no prior history of steroid use were included in the non-steroid-associated group, while those with a history of topical steroid use for more than 1 month, systemic steroid use regardless of duration, or confirmed use of other forms of steroids (intraarticular, etc.) at least once were classified into an all steroid-associated group. Participants in whom only the use of topical steroids was confirmed were classified into a topical steroid-associated group as a subgroup, while those who exclusively reported systemic steroid intake without the use of other steroid forms were categorized into a systemic steroid-associated group.

Statistical analysis

We performed all statistical analyses using the Statistical Package for the Social Sciences (SPSS, version 23.0; IBM Corp, Armonk, NY, USA). Continuous variables are presented as the mean and standard deviation (SD), while categorical variables are represented as frequencies. The χ^2 test was used to assess the correlation between steroid usage history and categorical or ordinal variables, including sex, comorbidity, and affected areas. To estimate the odds ratio (OR) and 95% confidence interval (CI) for the likelihood of eyelid involvement, an ordinal logistic regression model was performed.

RESULTS

A total of 192 patients with all steroid-associated rosacea, including 103 topical steroid-associated, 46 systemic steroid-associated, 7 other steroid form-associated, and 36 mixed steroid form-associated rosacea, were identified, alongside 264 non-steroid-associated patients. The average ages of both the all steroid-associated group (50.9 ± 16.8 years) and the topical steroid-associated group (51.5 ± 17.6 years) were higher compared with the non-steroid-associated group (46.8 ± 15.7, $p < 0.01$ and $p = 0.018$, respectively, **Table I**). However, there were no significant differences among the groups in terms of gender, BMI, and comorbidities, including diabetes. The

Table I. Demographic characteristics of non-steroid-associated and steroid-associated rosacea groups

Factor	Non-steroid-associated rosacea ($n = 264$)	All steroid-associated rosacea ($n = 192$)	*p*-value	Topical steroid-associated rosacea ($n = 103$)	*p*-value	Systemic steroid-associated rosacea ($n = 46$)	*p*-value
Age, years, mean ± SD	46.8 ± 15.7	50.9 ± 16.8	0.010*	51.5 ± 17.6	0.018*	49.9 ± 17.7	0.452
Gender, (%)							
Male	21.2	23.4	0.572	19.4	0.734	30.4	0.22
Female	78.8	76.6		80.6		69.6	
BMI, kg/cm^2, mean ± SD	22.9 ± 3.5	23.2 ± 4.1	0.519	22.7 ± 3.5	0.91	23.9 ± 4.1	0.279
Comorbidity, %							
Yes	71.9	77.6	0.172	74.8	0.74	86.9	0.061
No	28.1	22.4		25.2		13.1	
Previous steroid use							
Oral, *n* (%)	–	73 (38.0)	–	–	–	–	–
Topical, *n* (%)	–	137 (71.4)	–	–	–	–	–
Intralesional/intra-articular, *n* (%)	–	15 (7.8)	–	–	–	–	–
Steroid-use duration, day, mean ± SD	–	388 ± 740	–	427 ± 769	–	205 ± 324	–
Steroid-use duration, day, median	–	100	–	100	–	90	–

Other steroid forms and mixed steroid form use patients were not included for analysis due to low number of each form and heterogeneity in steroid usage history
BMI: body mass index; SD: standard deviation. *$p < 0.05$.

Table II. Clinical and laboratory features of non-steroid-associated and steroid-associated rosacea groups

	Non-steroid-associated rosacea ($n=264$)	All steroid-associated rosacea* ($n=192$)	p-value	Topical steroid-associated rosacea ($n=103$)	p-value	Systemic steroid-associated rosacea ($n=46$)	p-value
Rosacea type							
Erythematotelangiectatic, %	66.7	73.4	0.29	73.8	0.205	69.6	0.93
Papulopustular, %	28.4	30.2	0.39	29.1	0.849	41.3	0.08
Phymatous, %	8.3	3.1	0.048*	1.9	0.027*	2.2	0.16
Ocular, %	0.8	1.0	0.68	1.0	0.832	2.2	0.40
Lesion involved area							
Cheek, %	94.7	99.0	0.028*	99.0	0.13	97.8	0.34
Forehead, %	54.9	57.3	0.70	56.3	0.86	58.7	0.82
Nose, %	48.5	51.6	0.77	50.5	0.84	56.5	0.31
Chin, %	49.6	51.0	0.61	47.6	0.54	47.8	0.60
Eyelid, %	3.4	31.3	<0.01**	40.8	<0.01**	8.7	0.08
Peri-oral, %	11.4	7.8	0.25	7.8	0.38	8.7	0.34
Laboratory features							
Serum ACTH (pg/mL)	44.6	42.9	0.03*	45.4	0.402	40.3	0.087
% of ACTH > 60	20.0	16.3	0.86	15.7	0.652	19.6	0.663
Serum cortisol (μg/dL)	14.1	7.7	0.02*	7.8	<0.01**	7.3	<0.01**
% of cortisol < 5	3.0	27.7	<0.01**	26.2	<0.01**	34.8	<0.01**

Other steroid forms and mixed steroid form use patients were not included for analysis due to low number of each form and heterogeneity in steroid usage history.
*$p<0.05$, **$p<0.01$.

steroid usage duration in the all steroid-associated group had an average of 388 ± 740 days, with a median value of 100 days. Both the topical steroid-associated group (median: 150 days, mean: 427 ± 769 days) and the systemic steroid-associated group (median: 150 days, mean: 427 ± 769 days) demonstrated a heterogeneous distribution of steroid usage periods (Table I). Upon examination of rosacea types, it was observed that the all steroid-associated group and topical steroid-associated group had a lower prevalence of phymatous rosacea at 3.1% ($p=0.048$) and 1.9% ($p=0.027$), respectively, compared with the non-steroid-associated group at 8.3% (**Table II**). In comparison with the non-steroid-associated group, the odds ratio for eyelid involvement in the all steroid-associated group was 12.1 (95% CI; 5.8–25.2). Additionally, eyelid involvement was significantly more common in the topical steroid-associated group (40.8% vs 3.4%, $p<0.01$), but not in the systemic steroid- associated group (8.7%, $p=0.08$, Table I). Serum cortisol levels (normal range, 5–25 μg/dL) were lower in the all steroid-associated group at 7.7 μg/dL, compared with the non-steroid-associated group at 14.1 μg/dL ($p<0.01$), and the proportion of patients with serum cortisol levels lower than 5 μg/dL was also significantly higher in the all steroid-associated group (27.7% vs. 3.0%, $p<0.01$, **Fig. 1** and Table II). The HbA1c level was higher in the all steroid-associated group (6.4 vs 5.6%, $p=0.02$) and the topical steroid-associated group (7.0%, $p=0.04$) compared with the non-steroid-associated group (6.4 vs 5.6 %, $p=0.02$, Table SI). Other laboratory features demonstrated no statistically significant differences between the steroid-associated and non-steroid-associated groups (Table SI).

DISCUSSION

Steroid-associated rosacea is characterized by a high prevalence of eyelid involvement and low serum cortisol levels, which serve as distinguishing features when com-

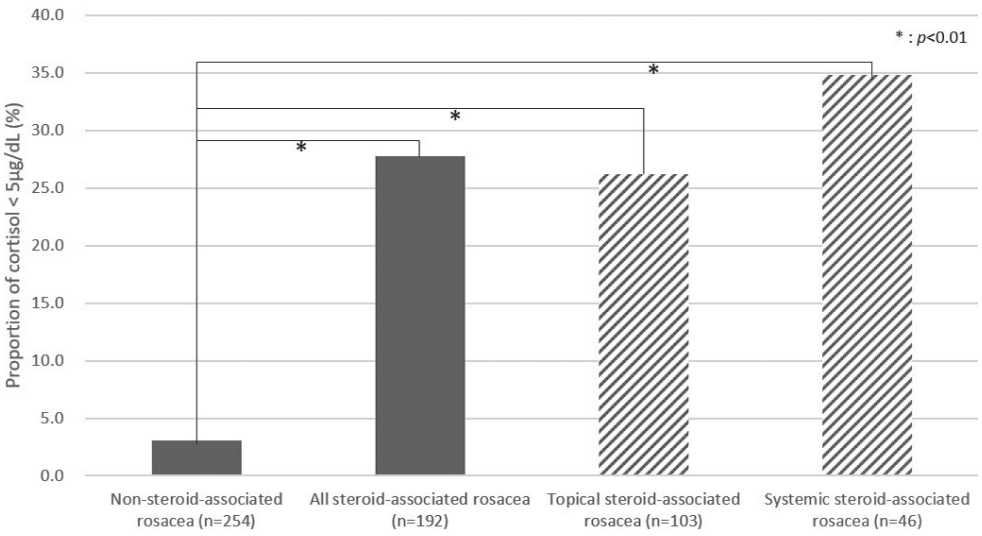

Fig. 1. Difference in proportion of patients with serum cortisol < 5 μg/dL according to rosacea groups.

pared with non-steroid-associated rosacea. Considering that topical steroid-associated rosacea also exhibits low serum cortisol levels, it is noteworthy that despite lower systemic absorption compared with systemic steroids, the continuous use of high-potency steroids increases the risk of secondary adrenal insufficiency (4, 7). Therefore, it can be speculated that both high potency and longer duration of use contribute to an elevated risk of rosacea development due to topical steroids. Frequent itching of periorbital skin and subsequent steroid application, as well as the thinness of the eyelid skin, may explain the clinical involvement observed (2, 8). When topical steroids are applied to the face, including the eyelids, direct exposure affects the facial skin, particularly due to the thinner stratum corneum and higher drug permeability of the eyelid skin, which may contribute to the characteristic occurrence of steroid-associated rosacea (9–11). Furthermore, in line with previous research findings, the cumulative dose and cumulative duration of topical steroid use are associated with the risk of developing diabetes (12). While this study is limited by its retrospective, single-institution design and the constraints of analysing a heterogeneous group with varied prior steroid usage, it stands as the initial examination of distinctive clinical and laboratory features in patients with steroid-associated rosacea. These findings should alarm dermatologists to suspect the history of topical steroid use in their patients and educate them regarding the risks associated with continued topical steroid use.

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The authors have no conflicts of interest to declare.

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