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Contact sensitization to cosmetic series of allergens in female patients with rosacea: A prospective controlled study in China

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Abstract

Background: Allergic contact dermatitis to cosmetics (ACDC) complicates the diagnosis and treatment of rosacea, and is increasingly observed in daily practice.

Aims: The present study aimed to identify the contact allergens responsible for ACDC in Chinese female rosacea patients with or without suspected ACDC (SACDC).

Methods: From a total of 1267 women with rosacea, 122 with SACDC, 145 without SACDC, and 100 age-matched healthy controls without rosacea or SACDC were examined on a voluntary basis. Skin patch tests with C-1000 cosmetic series (Chemotechnique Diagnostics, Malmo, Sweden) were conducted, including 20 selected allergens.

Results: Positive allergic reaction was found in 85.2% and 33.8% of SACDC and non-SACDC ($P < .001$), respectively, and 27.0% of healthy volunteers. Most reactions occurred at day 3, and the majority of all the examinees including normal controls reacted to more than 1 allergen. In SACDC patients, leading allergens were methylchloroisothiazolinone/methylisothiazolinone (28.7%), linalool hydroperoxide (27.1%), fragrance mix I (21.3%), methylisothiazolinone (17.2%), limonene hydroperoxides (16.4%), formaldehyde (14.8%), myroxylon pereirae (13.9%), and propolis (10.7%); the overall allergic reaction rate positively correlated with new onset of facial pruritus ($P < .001$). The occurrence of irritant contact reactions correlated with positive allergic reactions in rosacea patients with or without SACDC ($P = .032$ or $P < .001$, respectively).

Conclusions: Preservatives and fragrances are primary culprits for ACDC in Chinese female rosacea patients. Patch testing should be considered in the suspected patients.

KEYWORDS

allergic contact dermatitis, contact allergy, contact sensitization, cosmetic, rosacea

1 | INTRODUCTION

Allergic contact dermatitis to cosmetics (ACDC) is estimated to account for 2%-4% of all dermatologic consultations.¹ The true prevalence is probably much higher, probably also in China due to the rapid increase in cosmetic consumption and growing demand for

skincare in recent years. Results of patch testing in China showed allergic reactions to at least one cosmetic allergen in 28.9% of healthy university student volunteers, 18.8% of healthy cosmetics consumers, 9.8%-15.5% of eczema patients, 65.9% of female patients with facial cosmetic dermatitis, and 59.9% of patients with suspected ACDC (SACDC).²⁻⁵

Rosacea occurs predominately in genetically susceptible individuals aged 30–50 years with a female preponderance.⁶ Initiating or aggravating factors may include ultraviolet irradiation, alcohols, hot beverages, noxious cold and hot weather, and physical and emotional stress. In women with rosacea, a common complaint is an inexplicable aggravation of itchy erythema with or without burning or stinging in the course of application of skin care products, cosmeceuticals, or cosmetics, which generally ascribe to a controversial situation, the so-called “hypersensitive skin.” A high frequency of contact allergic reactions to cosmetic allergens has been demonstrated in rosacea patients.^{7–10} Relevant data are lacking in China.

This study was aimed to clarify the incidence of ACDC and to identify the responsible allergens in Chinese female rosacea patients with SACDC, with comparison to the non-SACDC rosacea patients and healthy control groups.

2 | MATERIALS AND METHODS

2.1 | Study population

The investigation was conducted in women with rosacea aged ≥ 18 years presented to the dermatology clinic of a tertiary comprehensive hospital in Chongqing, China, from January to December 2019, with 100 age-matched healthy volunteers (healthy volunteers were female participants without discernible skin changes or self-reported systemic diseases) as control. Diagnosis of rosacea was made by board-certified dermatologists following the criteria proposed by the National Rosacea Society (NRS) in the United States.¹¹

According to previous reports and a standard textbook,^{3,12} concurrent SACDC in rosacea patients with facial exposure to cosmetics met the following clues A, B and C. A) The degree of erythema of rosacea was aggravated, or erythema exceeded the edge of the original rosacea lesion, or well-demarcated erythema or eczematous eruptions localized to or outside the site of contact with cosmetics were newly developed. B) Patient experienced new onset or aggravation of itching sensation. C) Clues A and B lasted at least one week after cosmetic discontinuation, and they were not caused by other factors, such as sun exposure, hot bath, and topical medications for rosacea. Patient without clues A, B, and C was considered as non-SACDC.

Exclusion criteria included (a) pregnant or lactating women, (b) patient with history of severe allergic reaction or immediate contact reaction to cosmetics, (c) medical conditions that could compromise the evaluation of skin responsiveness, (d) patients with previous or current systemic diseases or skin diseases other than rosacea, such as acne, cutaneous lupus erythematosus, and diagnosis of cosmetic irritant contact dermatitis and atopic dermatitis, (e) use of systemic corticosteroids or any other immunosuppressive therapy in recent 3 months, or topical corticosteroids in the past 4 weeks, and (f) inability to return for follow-up. The study was approved by the Medical Ethics Committee of the Third Affiliated Hospital of

Chongqing Medical University, and written informed consent was obtained from all the participants at the time of recruitment.

2.2 | Patient profiles

A self-administered, structured questionnaire was used to collect data on general demographic variables (age, occupation, education background, ethnicity, height, and weight), health status (blood pressure, medical history, current medications, family history, and personal history of contact allergy), living habits (physical activity, alcohol intake, dietary habit, and sleep pattern), and the way of skincare and skincare products in all the participants. In rosacea patients, the information on dermatological conditions (Fitzpatrick's skin type, rosacea type and severity, course of rosacea, and rosacea-associated facial symptoms including itching, burning, and tingling) was inquired.

2.3 | Skin patch testing

All participants were patch-tested with the cosmetic series containing 20 allergens (C-1000 Series, Chemotechnique Diagnostics), following the manufacturer's instructions. The patches were removed at approximately 48 hours after their application. The initial, second, and delayed readings were performed at 30 minutes (day 2), 24 hours (day 3), and 5 days (day 7) after the removal of patches, respectively. The reactions were assessed following the recommendations by the “International Contact Dermatitis Research Group (ICDRG),” and morphologically positive patch test reactions (1+, 2+, or 3+) on either or both of the day 3 and day 7 are assessed as allergic. Well-demarcated erythematous reactions with or without morphologies of bullae and necrosis on the surface of the test area appeared within the first 48 hours but disappeared by 96 hours (decrecendo effect) were interpreted as irritant reactions.¹³ A positive patch test may be clinically relevant depending on current or past cosmetics exposures, and the relevance evaluation following the recommendations of the European Society of Contact Dermatitis.¹³ Postponing a patch test was arranged if the subjects had acute pruritic eczematous eruptions or met one of the conditions specified in Chinese expert consensus on clinical application of patch test (revised 2020).¹⁴

2.4 | Statistical analyses

Statistical analysis of the data compiled in Excel databank was conducted using SPSS/PC software (Version 19.0 for Windows; SPSS Inc, China). For descriptive analysis, the continuous and categorical variables were presented as mean (M) $\pm$ standard deviation (SD) and percentage (%), respectively. For comparison of demographic information and clinical characteristics between groups, the *chi-square* test or Student's *t* test was conducted. Fisher's exact test

was used to compare the positivity rate to each allergen in each group. Spearman's correlation analysis was used to determine the relationship between patch test results, with or without clinical parameters. A P value $< .05$ was accepted as the cutoff for statistical significance.

3 | RESULTS

3.1 | Subjects' characteristics

A total of 1267 women with rosacea were seen during the time of study, and 34.8% (441/1267) of them were with SACDC. On a voluntary basis, skin patch testing was completed in 122 rosacea patients with SACDC (age range: 18-58, mean $\pm$ SD 37.5 ± 16.6 years), 145 rosacea patients without SACDC (age range: 22-54, mean $\pm$ SD 38.2 ± 15.4 years), and 100 healthy controls (age range: 21-55, mean $\pm$ SD 37.9 ± 16.7 years). There was no statistical difference regarding age distribution, body mass index (BMI) index, ethnicity, education background, occupation, living, and skincare habits between the three groups ($P > .05$ for all variables).

3.2 | Clinical features of rosacea patients

In 122 patch-tested rosacea patients with SACDC, Fitzpatrick's skin type III was the predominant type, accounting for 61.5% of cases, with rosacea mainly involving the cheeks (90.2%, 110/122). No statistically difference was observed between rosacea patients with and without SACDC regarding Fitzpatrick's skin type, or the type or distribution of rosacea lesions ($P > .05$ for all variables). A significantly longer disease duration (34.5 ± 13.2 vs 21.5 ± 11.8 months, $P < .001$) and a higher proportion with ocular involvement (40.2% vs. 19.3%, $P = .006$) were found in SACDC rosacea patients than those without SACDC. In general inquiry before patch testing, facial discomforts were much more common in rosacea patients with SACDC than without SACDC ($P < .05$ for all variables). Detailed clinical characteristics are summarized in Table 1.

3.3 | Allergic contact reactions

As showed in Figure 1, at least one positive allergic contact reaction (PACR) to the skin patch testing was observed in 104 (85.2%) rosacea patients with SACDC, which was significantly higher than that in 49 (33.8%) without SACDC ($P < .001$) and in 27 (27.0%) healthy controls ($P < .001$). In the SACDC rosacea group, 29 (23.8%) cases reacted only to 1 allergen, 28 (22.9%) to 2 allergens, and 47 (38.5%) to 3 or more. Among rosacea patients, PACR to 1, 2, or more contact allergens were all more common in the SACDC group than the non-SACDC group ($P = .013$, $= .027$, and $< .001$, respectively). There was no difference in the overall PACR rate, rate of PACR to 1, 2, or more contact allergens between rosacea patients without SACDC

TABLE 1 Clinical findings of rosacea subjects

Items	Rosacea patients		P value
	with SACDC	without SACDC	
No. of subjects	122	145	
Age (y)	37.5 ± 16.6	38.2 ± 15.4	.721
Disease course (months)	34.5 ± 13.2	21.5 ± 11.8	<.001
Fitzpatrick's skin type			
II	33 (27.0)	42 (28.9)	.794
III	75 (61.5)	88 (60.7)	.949
IV	14 (11.5)	15 (10.4)	.791
Lesion distribution			
Cheeks	110 (90.2)	128 (88.3)	.906
Nasal or perioral	12 (9.8)	17 (11.7)	.658
Rosacea type			
Erythematotelangiectatic	63 (51.6)	72 (49.6)	.853
Papulopustular	40 (32.8)	52 (35.9)	.713
Phymatous	19 (15.6)	21 (14.5)	.831
Ocular involvement	49 (40.2)	28 (19.3)	.006
With facial symptoms			
New onset of pruritus	51 (41.8)	37 (25.5)	.042
Aggravation of pruritus	71 (58.2)	33 (22.8)	<.001
Burning	64 (52.5)	29 (20.0)	<.001
Tingling	42 (34.4)	28 (19.3)	.033

Note: Abbreviation: SACDC, suspected allergic contact dermatitis to cosmetics.

Data are presented as mean $\pm$ SD or number (%).

and healthy control group ($P = .410$, $P = .573$, $P = .475$, and $P = .764$, respectively).

Of the 246 PACRs observed in the SACDC rosacea group, 47 (19.1%) were "3+", 166 (67.5%) were "2+", and 33 (13.4%) were "1+". A total of 121 and 51 PACRs were observed in the non-SACDC rosacea group and the healthy controls, respectively, and "2+" PACRs (58.7%) and "1+" PACRs (76.5%) were most common in the two groups, respectively. Among the PACRs, 85.4% (210/246) of the SACDC, 71.1% (86/121) of the non-SACDC, and 84.3% (43/51) of the healthy controls presented PACR at day 3. The percentage of PACR to all the applied allergens in C-1000 cosmetic series in different studied groups are shown in Table 2. The most common allergens demonstrated in SACDC rosacea patients was methylchloroisothiazolinone (MCI)/methylisothiazolinone (MI) (28.7%, 35/122), followed by linalool hydroperoxide (lin-OOHs) (27.1%, 33/122), fragrance mix I (21.3%, 26/122), MI (17.2%, 21/122), limonene hydroperoxides (lim-OOHs) (16.4%, 20/122), formaldehyde (14.8%, 18/122), myroxylon pereirae (13.9%, 17/122), and propolis (10.7%, 13/122), with statistically significant higher percentages as compared to the non-SACDC patients ($P < .05$ for all variables). There was no statistically significant difference in the PACRs to the individual allergens between the non-SACDC rosacea patients and healthy controls ($P > .05$ for all variables).

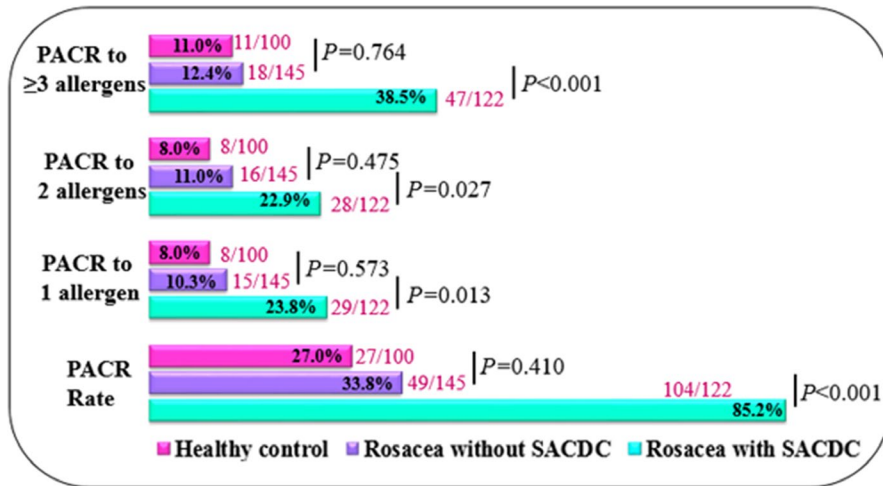


FIGURE 1 Rates of positive allergic contact reaction (PACR) to cosmetic allergens. SACDC, suspected allergic contact dermatitis to cosmetics

In addition, concomitant sensitization was most commonly observed in SACDC rosacea patients reactive to MI and MCI/MI, followed by lin-OOHs and lim-OOHs, which was significantly higher than that in non-SACDC rosacea patients (12.3% vs 4.8%, $P = .042$; 11.5% vs 3.5%, $P = .018$) (Table 3).

In rosacea patients with SACDC, there was no statistically significant association between the presence of PACR and the age, disease duration, occupation, skin type, rosacea type, or ocular involvement ($P > .05$ for all variables), except the positive association with new onset of pruritus ($P < .001$). Finally, correlation between the clinical symptoms and exposure to positive allergens containing cosmetics was confirmed in 34.4% (42/122) of the SACDC rosacea cases. These patients refused further proof by repeated open application test with their own cosmetics containing the suspected allergens.

3.4 | Irritant contact reactions

At least one positive irritant reaction was observed in 66 (54.1%) rosacea patients with SACDC, which was higher than that in 42 (28.9%) without SACDC ($P = .007$) and in 21 (21.0%) healthy controls ($P < .001$). Correlation analysis showed association between irritant reaction and PACR in SACDC patients ($P = .032$) or in the non-SACDC patients ($P < .001$), whereby no association was found between irritant reaction and the numbers of the PACR ($P = .231$ and $.245$, respectively). Such association with the presence of PACR ($P = .714$) or PACR numbers ($P = .320$) was not detected in the controls. Positive irritant reaction was most common in 27 SACDC patients with allergic to lin-OOHs and in 11 non-SACDC patients to MCI/MI. In total, 82 and 50 irritant reactions were recorded in the SACDC and non-SACDC rosacea group, respectively, as compared to 24 in the healthy controls (Table 4). Paraben mixture, lin-OOHs, and lim-OOHs were the first three agents causing irritant reactions in all the three subgroups of examinees. Double reactions (irritant reactions to two allergens simultaneously) were observed only in lin-OOHs/ lim-OOHs, as well as MI + MCI/ MI (Table 4).

4 | DISCUSSION

In China, rosacea affects around 3.48% of the general population and 3.40% of fresh students aged 18.3 ± 0.6 years.^{15,16} For aesthetic or therapeutic purposes, cosmetics are more widely used in rosacea patients than general population. Based on a standard textbook,¹² coexistence of ACDC should be considered when the rosacea patients (especially women) present with clinical clues as described before in the course of application of cosmetics. Patch testing with cosmetic allergens is a gold standard aid in the identification of relevant allergens in patients with indicative of SACDC. Individuals with cosmetic contact allergy, in particular rosacea patients with sensitive and inflamed skin, tend to display more visible contact reactions to cosmetic allergens.^{7,8} The so-called sensitive skin in rosacea patients is so far ill-defined and less studied. It can be partially explained by the damaged epidermal barrier, which allows increased penetration of irritants and allergens.¹⁷ Threshold for contact reaction is also reduced by epidermal inflammation and increased irritability of cutaneous nerve endings.¹⁸

In the present study, cosmetic contact sensitivity was confirmed in 57.3% (153/267) of Chinese adult women with rosacea. By comparison, it is reported that 48.7% of Germany women with rosacea were sensitized to DKG standard series including cosmetic allergens,¹⁹ and 30.8% of Turkish rosacea patients (5 men and 60 women) were allergic to cosmetic series including 57 allergens.⁸ Specifically, SACDC was found in 34.8% (441/1267) of our rosacea patients, and PACR was identified in 85.2% (104/122) of the patch-tested women with SACDC during one-year observation. ACDC in rosacea was first evaluated in 4 male and 25 female patients from Italy, who described intolerance to cosmetics and/or topical medications, and 39.7% of them were found to be sensitized to Gruppo Italiano Ricerca Dermatiti da Contatto e Ambientali (GIRDCA) standardized series including 20 allergens.²⁰ In two independent clinical studies in Hungary, skin patch test detected contact sensitivity in 37.8% of 143 and 35.4% of 82 rosacea patients (the majority are women), respectively, who experienced worsening of skin symptoms via topical treatments or cosmetics.^{9,10} On the other hand, PACR in 33.8% (49/145) of non-SACDC rosacea women in our study was much lower

TABLE 2 Total PACRs and patch test positivity in rosacea patients and control subjects

Items	Rosacea with SACDC (n = 122)	Rosacea without SACDC (n = 145)	Healthy control (n = 100)
Total PACRs	246	121	51
Allergens (concentration, %)		<i>P</i> value ^b	<i>P</i> value ^c
Fragrance			
1. Propolis (10.0)	13 (10.7)	6 (4.1)	.045
2. FM I (8.0)	26 (21.3)	14 (9.7)	.023
3. FM II (8.0)	9 (7.4)	5 (3.4)	.174
4. Lin-OOHs (1.0)	33 (27.1)	15 (10.3)	.003
5. Myroxylon pereirae (25.0)	17 (13.9)	8 (5.5)	.033
6. Lim-OOHs (0.3)	20 (16.4)	6 (4.1)	.002
7. Ylang oil (2.0)	6 (4.9)	7 (4.8)	.974
8. Cinnamyl aldehyde (1.0)	1 (0.8)	2 (1.4)	.669
Preservative			
9. Paraben mixture (15.0)	8 (6.6)	4 (2.7)	.154
10. Quaternium-15 (1.0)	5 (4.1)	2 (1.4)	.178
11. Diazolidinyl urea (2.0)	4 (3.3)	1 (0.7)	.128
12. MCI/MI (0.02) ^a	35 (28.7)	14 (9.7)	<.001
13. MI (0.2) ^a	21 (17.2)	12 (8.3)	.041
14. Formaldehyde (1.0) ^a	18 (14.8)	8 (5.5)	.022
Surfactant			
15. Decyl glucoside (5.0)	4 (3.3)	3 (2.1)	.548
Emulsifier			
16. Amerchol L 101 (50.0)	5 (4.1)	2 (1.4)	.178
Solvent			
17. Benzyl salicylate (1.0)	8 (6.6)	3 (2.1)	.078
Lubricant			
18. IMA (20.0)	2 (1.6)	3 (2.1)	.800
Disinfectant			
19. Glutaraldehyde (1.0)	8 (6.6)	3 (2.1)	.078
The other			
20. Sesquiterpene lactone mix (0.1)	3 (2.5)	3 (2.1)	.834

Note: Abbreviations: FM, fragrance mix; IMA, isopropyl myristic acid ester; Lim-OOHs, limonene hydroperoxide; Lin-OOHs, linalool hydroperoxide; MCI, methylchloroisothiazolinone; MI, methylisothiazolinone; PACR, positive allergic contact reaction; SACDC, suspected allergic contact dermatitis to cosmetics.

All allergens in petrolatum, except where indicated: ^ain water. Data are presented as number (%).

^bCompared to rosacea with SACDC, ^ccompared to rosacea without SACDC.

than that of 67.7% observed in 68 non-SACDC women with rosacea in Turkey.⁷ To compare the prevalence of cosmetic contact allergy among different studies, many variables must be considered, such as the type and number of allergens, the ethnic background, gender, personal behavior, and type and severity of rosacea (Table 5).

In terms of contact allergens reported in literature,^{7-10,19} our rosacea patients with SACDC showed a significantly higher prevalence of contact sensitization to fragrance mix I (4.8 ~ 8.8% vs 21.3%), myroxylon pereirae (6.1 ~ 10.4% vs 13.9%), propolis (2.8%

vs 9.8%), MCI/MI (2.9% vs 28.7%), quaternium-15 (0.9% vs 4.1%), and paraben mix (1.9% vs 6.6%). One possible explanation is that our study examined only women, who generally have a higher frequency of cosmetic use, and with a higher risk of sensitization. To correctly detect MI contact allergy, the routine separate testing of MI 0.2% aq was recommended because of low concentration (25%) of MI in MCI/MI 0.02% aq. Surprisingly, only 15 among the 35 SACDC cases with PACR to MCI/MI also tested positive to MI, indicating MCI contact sensitization may be underestimated

Allergens	Rosacea patients			Healthy control (n = 100)	P value ^b
	With SACDC (n = 122)	Without SACDC (n = 145)	P value ^a		
Lim-OOHs + Lin-OOHs	14 (11.5)	5 (3.5)	.018	2 (2.0)	.515
Myroxylon pereirae + propolis	9 (7.4)	4 (2.8)	.097	2 (2.0)	.712
Myroxylon pereirae + FM II	5 (4.1)	3 (2.1)	.347	1 (1.0)	.523
FM I + FM II	6 (4.9)	4 (2.8)	.373	3 (3.0)	.914
Ylang oil + benzyl salicylate	3 (2.6)	2 (1.4)	.525	0 (0.0)	.242
MI + MCI/MI	15 (12.3)	7 (4.8)	.042	2 (2.0)	.264
Diazolidinyl urea + formaldehyde	4 (2.5)	0 (0.0)	.061	0 (0.0)	1.000

Note: Abbreviations: FM, fragrance mix; Lim-OOHs, limonene hydroperoxide; Lin-OOHs, linalool hydroperoxide; MCI, methylchloroisothiazolinone; MI, methylisothiazolinone. Data are presented as number (%); SACDC, suspected allergic contact dermatitis to cosmetics.

^aComparison between SACDC and non-SACDC rosacea patients.

^bComparison between non-SACDC rosacea patients and control subjects.

TABLE 3 The most common concomitant sensitizations in different subgroups

Irritants	Rosacea patients			Healthy control (n = 100)	P value ^b
	With SACDC (n = 122)	Without SACDC (n = 145)	P value ^a		
Paraben mixture	15 (12.3)	8 (5.5)	.072	4 (4.0)	.606
Formaldehyde	11 (9.0)	5 (3.4)	.073	2 (2.0)	.515
MCI/MI	11 (9.0)	5 (3.4)	.073	3 (3.0)	.851
MI	8 (6.6)	6 (4.1)	.402	2 (2.0)	.369
Diazolidinyl urea	5 (4.1)	3 (2.1)	.347	2 (2.0)	.971
Quaternium-15	2 (1.6)	4 (2.8)	.548	1 (1.0)	.348
Lin-OOHs	14 (11.5)	9 (6.2)	.162	5 (5.0)	.705
Lim-OOHs	12 (9.8)	7 (4.8)	.141	4 (4.0)	.769
Sesquiterpene lactone mix	4 (3.3)	3 (2.1)	.548	1 (1.0)	.523
MI + MCI/MI	7 (5.7)	3 (2.1)	.130	1 (1.0)	.523
Lin-OOHs + Lim-OOHs	9 (7.4)	5 (3.4)	.174	2 (2.0)	.515

Note: Abbreviations: Lim-OOHs, limonene hydroperoxide; Lin-OOHs, linalool hydroperoxide; MCI, methylchloroisothiazolinone; MI, methylisothiazolinone. Data are presented as number (%); SACDC, suspected allergic contact dermatitis to cosmetics.

^aComparison between SACDC and non-SACDC rosacea patients.

^bComparison between non-SACDC rosacea patients and control subjects.

TABLE 4 All irritant reactions in rosacea patients and control subjects

in such patients. Another noteworthy is the higher rate of contact allergy to lin-OOHs (27.1%), lim-OOHs (16.4%), and formaldehyde (14.8%) in our rosacea patients with SACDC, which has been scarcely observed. Hydroperoxide of linalool and limonene is widely used in cosmetics, household products, and 90 ~ 97% of essential oils, which showed frequent co-sensitization.²¹ The presence of concomitant or multiple allergic reactions in rosacea patients was not reported in previous studies and seemed not to

be a rare event based on our observations, especially the co-sensitization to MI + MCI/MI and lin-/lim-OOHs. Together with diazolidinyl urea (formaldehyde releaser) and decyl glucoside (non-ionic surfactant), lin-OOHs and lim-OOHs are included in the recommended additions to the European baseline series in 2019,²² implying the importance of emerging allergens in ACDC.

It is noteworthy that the groups of MI + MCI/MI and lin-/lim-OOHs were the most common agents responsible for both allergic

TABLE 5 Comparison of contact allergy to cosmetics in rosacea patients from different studies

First author, year	Country	Patients	M/F	Allergen No.	Rate of CH
Jappe U, 2008 ¹⁷	Germany	19 SACDC	40/38	DKG series	51.3% in M; 48.7% in F
Erdogan HK, 2018 ⁸	Turkey	Unclear	5/60	57	30.8%
Corazza M, 1997 ¹⁸	Italy	Intolerance ^a	4/25	20	39.7%
Pónyai G, 2012 ⁹	Hungary	Worsening ^b	14/68	35	35.4%
Diczig B, 2018 ¹⁰	Hungary	Worsening ^b	143 in total	38	37.8%
Present study	China	SACDC	0/122	20	85.2%
Ozbacivan O, 2020 ⁷	Turkey	Non-SACDC	35/68	49	45.7% in M; 67.7% in F
Present study	China	Non-SACDC	0/145	20	33.8%

Note: Abbreviations: CH, cosmetic hypersensitivity; F, female; M, male; SACD, suspected allergic contact dermatitis; SACDC, SACD to cosmetics.

^aIntolerance to cosmetics and/or topical medications.

^bWorsening of skin symptoms via topical treatments or cosmetics.

and irritant reactions in our patients. A possible reason is that the same concentrations of tested substances were used in our settings, whereas irritant thresholds in patients with rosacea were declined.^{18,21} Further testing with serial dilutions of the allergens may improve the diagnostic performance. Moreover, the positive correlations between allergic and irritant reactions in our rosacea patients with or without SACDC may be closely associated with the disease states and may lend further support to the assumption that rosacea skin is overreactive and prone to higher irritant contact reactions to cosmetics.¹

Sensitive skin syndrome is a controversial ill-define entity, and the prevalence was estimated to be 1%-5% in rosacea patients.²³ Our results with allergic reactions in 57.3% (153/267) and irritant reactions in 40.4% (108/267) indicated that the "sensitive skin" may be much more common in the Chinese patients with rosacea, and overlap or associate with contact dermatitis. The observation of concomitant sensitizations and higher irritant reactions in most rosacea patients with SACDC may be related to the pathogenesis in this specific population. Genetic predisposition, locally impaired epidermal barrier, inflammation of rosacea, pre-existing skin diseases such as atopic dermatitis, co-exposure to multiple allergens, and cross-allergic reaction among allergens can all contribute to an increased incidence of contact sensitization or irritative reaction to cosmetics.^{24,25} Further studies are required to clarify the relation and interaction between sensitive skin syndrome and rosacea.

There are many limitations in the present study. The results of a hospital-based study usually recruit patients with more severe disease (rosacea) and cannot reflect the situation in general population. Only a small portion (267/1267, 21.1%) of the rosacea patients in our series underwent skin patch testing. Contact sensitization does not mean contact dermatitis, and the definite diagnosis can be confirmed through avoidance of culprit allergens, follow-up evaluation, or provocation tests, which failed in

our series. Differentiation between irritant and allergic reactions is not always straightforward. Male patients with rosacea were excluded in this study; therefore, a possible gender difference cannot be elucidated. As standard series and not all the recommended allergens in C-1000 cosmetic series were tested, misdiagnosis or under-diagnosis cannot be excluded.

In conclusion, our study is the first large-scale systematic evaluation and analysis of contact sensitization to cosmetics in Chinese female patients with rosacea in the presence or absence of SACDC. Due to the high positive rate of contact sensitization in our patients, attention should be given to patients with exacerbation of clinical symptoms or manifestations, and skin patch testing is strongly recommended.

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CONFLICT OF INTEREST

None declared.

AUTHOR CONTRIBUTION

BangtaoChen wrote the original draft. Fubing Yu investigated the data. WenChieh Chen wrote, reviewed, and edited the manuscript. Zhengqiu Yao and Xi Yang investigated the data and curated the data. Daojun Zhang designed methodology. Fei Hao conceptualized and supervised the data.

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