Original Article

Clinical indicators of rosacea progression: a topographic evaluation according to subtype and severity

玫瑰痤瘡進展的臨床指標：根據亞型和嚴重度進行面部分佈評估

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In this study, 704 patients were analyzed and classified into four subtypes (erythematotelangiectatic (ETR), papulopustular (PPR), combined (ETR + PPR), phymatous (PHY)). The most common subtype was ETR (55.7%), followed by combined type (22.6%). The cheek was the most commonly affected site (89.9%), followed by the nose (56.5%), glabella (37.8%), nasolabial fold (17.2%) and periorbital area (9.8%). The glabella was significantly more frequently affected in the combined type (69.2%) than in ETR (28.3%), regardless of severity. The response rate was significantly different between ETR and combined type (10.9% vs 26.0%). In Korean patients with rosacea, pure PPR is much less common than the combined subtype. Glabellar and nasal involvement can be an early marker of subtype transition from ETR to the combined subtype.

本研究對704例患者進行分析，將其分爲紅斑血管擴張型、丘疹膿皰型、混合型和鼻瘤型四個亞型。當中最常見的亞型是紅斑血管擴張型（55.7%），其次是混合型（22.6%）。最常受影響的部位是面頰（89.9%），其次是鼻（56.5%）、眉間（37.8%）、鼻唇褶（17.2%）和眼週邊位置（9.8%）。無論嚴重程度如何，混合型（69.2%）的眉間影響率遠高於紅斑血管擴張型（28.3%）。而紅斑血管擴張型與混合型的治療成效有顯著性差異（10.9%對26.0%）。在韓國的玫瑰痤瘡患者中，純紅斑血管擴張型比混合型（卽從紅斑血管擴張型進展的丘疹膿皰型）亞型來得罕見。眉間和鼻的影響則可能是從紅斑血管擴張型演變爲混合型的早期徵兆。

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Introduction

Rosacea, a chronic inflammatory skin disorder, is fairly common with a prevalence of up to 12% of the Caucasian population.[1] It is also common in the Asian countries. In a recent study from three Korean university hospitals a 46% increase in the number of rosacea patients between 2013 to 2016 was reported (unpublished data). Clinically, rosacea mainly affects the central

portion of face, and its symptoms appear in various combinations from flushing, telangiectasia to inflammatory lesions such as papules.[2] The overlap and progression between each subtype varies widely among different patients, and there are no good clinical markers to predict rosacea progression.[3] Histologically, dilatation of superficial blood vessels is characteristic, and infiltration of inflammatory cells around blood vessels can be seen in varying degrees. Also, it may show dermal oedema or dermal fibrosis.[4] Due to these various manifestations, it is difficult to formulate coherent diagnostic criteria. The National Rosacea Society Expert Committee (NRSEC) suggested diagnostic criteria for rosacea in 2002.[5] Rosacea can be diagnosed if one or more of the following criteria are present: flushing, persistent erythema, papules and pustules, facial telangiectasia together with symptoms of burning, plaque, dryness, oedema, or eye symptoms.

In addition, NRSEC divided rosacea into four subtypes; erythematotelangiectatic rosacea (ETR), inflammatory papulopustular rosacea (PPR), phymatous rosacea (PHY) and ocular rosacea. Subtypes were classified according to the characteristic location and symptoms; however, these four subtypes are not clearly distinguishable and many patients have mixed features.[5] Apart from the diagnostic criteria, NRSEC suggested the grading system of rosacea severity. As with the subtype classification described above, the severity of the rosacea often lies on a spectrum, so it is not easy to assess the severity clearly.[6] Due to these difficulties in subtype classification and severity assessment, the corresponding areas of the face and the progression in these subtypes is not clearly defined. The purpose of this study was to investigate the topographical and prognostic differences according to the subtype and severity of rosacea.

Methods

We analysed the electronic medical record (EMR) of our institution retrospectively. This investigation was approved by the internal Institutional Review Board of Boramae Medical Center. Among the patients from January 2010 to December 2015, we searched for those who were diagnosed with rosacea according to NRSEC criteria. The age, gender, disease duration, medical photos of the patients were obtained from the EMR. If any of these factors were missing, the case was discarded. The incidence of diabetes mellitus, hypertension, thyroid disease and solid cancer with rosacea was searched. We also investigated for concomitant cutaneous diseases such as seborrheic dermatitis and perioral dermatitis which have a similar appearance with rosacea. The subtype, severity and affected sites of rosacea were evaluated using the initial medical photographs. The treatment response was assessed from the photographs of previous consultations. Of the four subtypes of rosacea in NRSEC classification (ETR, PPR, PHY, ocular rosacea), the ocular type was excluded owing to difficulties of assessing ocular rosacea from medical images. In addition, we designated the cases with combined features of erythema and telangiectasia with papules and pustules as the combined type. Pure ETR and pure PPR were designated to ETR type and PPR type, respectively. Three dermatologists reached a consensus on the subtype of rosacea. Severity was graded as absent, mild, moderate, or severe (0-3) according to the standards of NRSEC.[6] In the combined type, the severity was assessed as the grade of the dominant type (ETR or PPR). The clinical improvement was evaluated by using a numerical scale where 0 was defined as a fair response (less than 50% clearance of visible skin lesions), 1 as good response (more than 50% clearance), and 2 as excellent response (almost complete clearance). Three dermatologists

independently performed a blind evaluation of the severity and the treatment response using the grading system mentioned above. The difference in the location of the rosacea lesions investigated. As the site differences could depend on the severity, not purely on the subtype, we stratified the data by severity. If the severe cases were weighted into a specific subtype, the result could be distorted as if there were topographic differences according to subtype.

Statistical analysis

All analyses were performed using SPSS version 22 (IBM, New York, NY, USA). Categorical variables among each subtype were analysed using the Chi-square test or the linear by linear association test. Statistical significance was defined as p value <0.05.

Results

A total of 812 patients with rosacea were retrieved through the review of EMR. Of these 812 patients, 704 patients met all inclusion criteria of this study. The mean age was 50.5 years (range, 9-86), and a male to female ratio was 1:1.99. Female predominance was observed in ETR and combined type. The mean duration of rosacea at the first visit was 40.7 months. Most patients (67.2%) had less than 1 year of disease duration. Table 1 shows the demographics of the patients and duration of rosacea. The age and duration of the disease were not significantly different among subtypes. The most common subtype was ETR (55.7%), followed by combined type (22.6%), PHY (11.4%) and PPR (10.4%). About two-thirds of patients with papules and pustules also had erythema and telangiectasia. Of all patients, 78.3% had erythematous and telangiectatic components, as calculated by adding the number of ETR and combined type patients.

Topographic differences among subtypes

The cheek was the most commonly affected site (89.9%), followed by the nose (56.7%), glabella (37.8%), nasolabial fold (17.2%) and periorbital area (9.8%). Details about affected area according to subtype is given in Table 2. The glabella was significantly more frequently affected in combined type (69.2%) than in ETR (28.3%), regardless of severity (Table 3). The same trend was seen with nasolabial involvement (39.0% in combined type and 10.5% in ETR, respectively, data not shown). Glabella and nasolabial fold involvement is evident in the combined type (Figure 1).

Topographic differences according to severity

The disease severity was designated as three non-consecutive groups (mild, moderate, severe) for the purpose of analysis; however in reality, these severity groups formed a continuous spectrum. The correlation between the lesion site and severity was analysed by linear by linear association.

The nose was affected in 37.2% of mild patients, 68.5% of moderate patients and 90.5% of severe patients implying that the nasal area was significantly more frequently invaded with higher severity (p<0.0001). A similar tendency was also observed in glabella, nasolabial fold and periorbital area; all p values were less than 0.0001 (Table 4).

Treatment response rate according to subtype

Treatment response rate was graded as fair, good or excellent improvement by the aforementioned criteria. The excellent response rate was significantly higher in the combined type (26.0%)

than in the ETR (10.9%) (p<0.0001). Similar difference was seen between PPR (41.5%) and ETR (10.9%) (p<0.0001). As for treatment, ETR was treated topically with metronidazole gel in the morning and pimecrolimus cream at night, plus oral antihistamine and/or doxycycline (50-100 mg/day). PPR and combined type was treated with topical metronidazole and oral antihistamine and doxycycline (50-200 mg/day) or isotretinoin (10-20 mg/day). Doxycycline was usually started at 100 or 200 mg/day and slowly tapered to 50 mg/day or 50 mg/every other day over 3-6 months. Patients were advised to resume doxycycline upon recurrence. Isotretinoin was used as a second-line drug in patients not responding to doxycycline.

Influence of associated disease

There was no significant association between rosacea and other diseases (diabetes mellitus, hypertension, thyroid diseases, solid cancers) was investigated. The co-existence of seborrheic

dermatitis did not affect the site of the lesions (p=0.089).

Discussion

Rosacea is a chronic inflammatory skin disorder, which is characterised by interfollicular skin erythema, flushing and papules in the central face. However, there is no definite standard or widely recognised definition of rosacea and its subtypes.[5,6] In this circumstance, the relative prevalence of each subtype and information on the relationship between subtypes has been well established. The National Rosacea Society (NRS) classification system recognises the possible overlapping of subtypes.[5,7,8] According to this classification system, papules and pustules can appear with or without erythema. It is unclear whether pure PPR subtype which is not associated with erythema is a genuine rosacea. As well as sparse information on subtype characteristics, the data on topographic preference according to subtype is limited. We planned this study to assess the

Table 1. Demographics of patients according to subtype of rosacea

Demographic feature	Rosacea subtype				
	ETR n=392 (55.7%)	PPR n=73 (10.4%)	Combined n=159 (22.6%)	PHY n=80 (11.4%)	Total n=704
Age (years)					
Mean±SD	50.3±15.7	53.1±12.8	49.3±14.6	51.2±16.3	50.5±15.2
Range	9-84	21-80	14-86	18-79	9-86
Age distribution, n (%)					
<31	48 (12.2)	3 (4.1)	15 (9.4)	11 (13.8)	77 (10.9)
31-50	131 (33.4)	24 (32.9)	65 (40.9)	26 (32.5)	246 (34.9)
51-70	186 (47.4)	40 (54.8)	66 (41.5)	31 (38.8)	323 (45.9)
>71	27 (6.9)	6 (8.2)	13 (8.2)	12 (15)	58 (8.2)
Duration of rosacea (months)					
Mean±SD	48.5±87.7	27.2±50.6	32.6±43.5	37.1±50.6	40.7±71.5
Sex, n (%)					
Male	113 (28.8)	25 (34.2)	42 (26.4)	55 (68.8)	235 (33.4)
Female	279 (71.2)	48 (65.8)	117 (73.6)	25 (31.3)	469 (66.6)

ETR, erythematotelangiectatic rosacea; PPR, papulopustular rosacea; PHY, phymatous rosacea.

Table 2. Topographic differences according to subtype

Location				ETR	PPR	Combined type	PHY	Total
						Subtype		
Cheek	No	n		14	7	1	49	71
		% in subtype		3.6%	9.6%	0.6%	61.3%	10.1%
	Yes	n		378	66	158	31	633
		% in subtype		96.4%	90.4%	99.4%	38.8%	89.9%
Nose	No	n		235	26	44	0	305
		% in subtype		59.9%	35.6%	27.7%	0.0%	43.3%
	Yes	n		157	47	115	80	399
		% in subtype		40.1%	64.4%	72.3%	100.0%	56.7%
Glabella	No	n		281	38	49	70	438
		% in subtype		71.7%	52.1%	30.8%	87.5%	62.2%
	Yes	n		111	35	110	10	266
		% in subtype		28.3%	47.9%	69.2%	12.5%	37.8%
Nasolabial fold	No	n		351	59	97	76	583
		% in subtype		89.5%	80.8%	61.0%	95.0%	82.8%
	Yes	n		41	14	62	4	121
		% in subtype		10.5%	19.2%	39.0%	5.0%	17.2%
Periorbital area	No	n		356	67	133	79	635
		% in subtype		90.8%	91.8%	83.6%	98.8%	90.2%
	Yes	n		36	6	26	1	69
		% in subtype		9.2%	8.2%	16.4%	1.3%	9.8%

ETR, erythematotelangiectatic rosacea; PPR, papulopustular rosacea; PHY, phymatous rosacea.
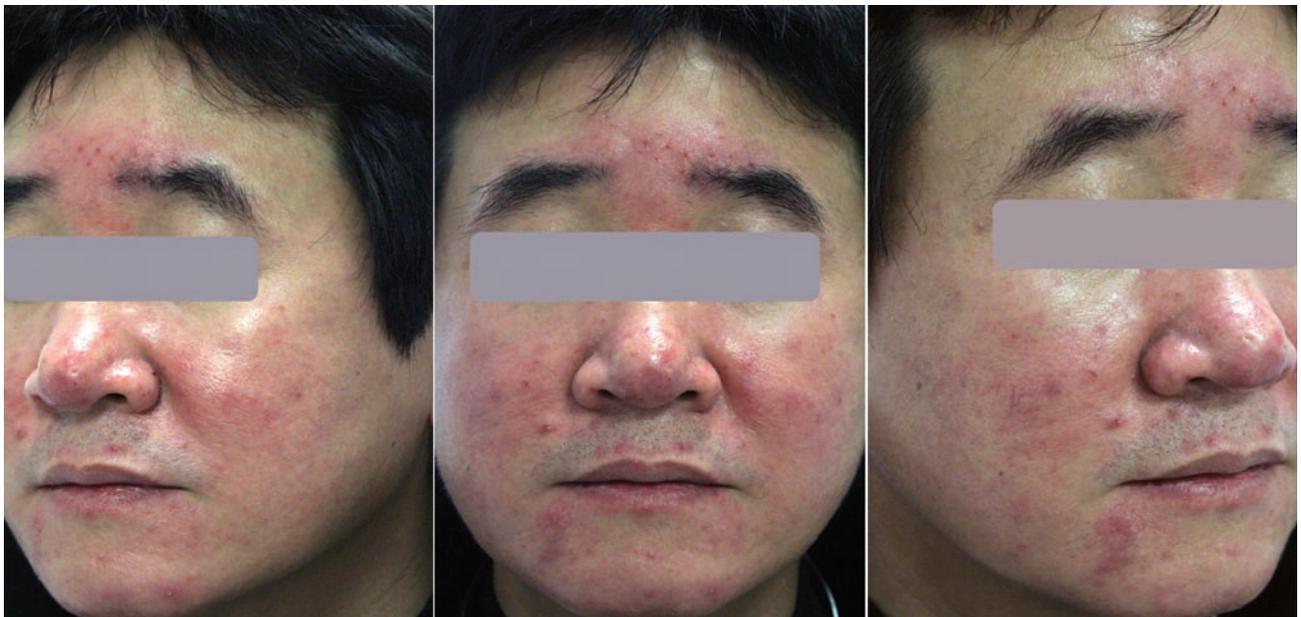

Figure 1. Glabellar and nasolabial fold involvement in combined type rosacea.

Table 3. Differential glabellar involvement in ETR and combined type

Severity	Location			Subtype		P value
				ETR	Combined type	
Mild	Glabella	No	n	200	23	
			% in subtype	89.3%	71.9%	
		Yes	n	24	9	
			% in subtype	**10.7%**	**28.1%**	0.011
Moderate	Glabella	No	n	73	23	
			% in subtype	54.9%	27.4%	
		Yes	n	60	61	
			% in subtype	**45.1%**	**72.6%**	0.0001
Severe	Glabella	No	n	8	3	
			% in subtype	22.9%	7.0%	
		Yes	n	27	40	
			% in subtype	**77.1%**	**93.0%**	0.047
Total	Glabella	No	n	281	49	
			% in subtype	71.7%	30.8%	
		Yes	n	111	110	
			% in subtype	**28.3%**	**69.2%**	0.0001

ETR, erythematotelangiectatic rosacea.

Table 4. Topographic differences according to severity of rosacea

			Subtype			Total	P value (Linear by linear association)
			Mild	Moderate	Severe		
Nose	No	n	209	87	9	305	
		% in Severity	62.8%	31.5%	9.5%	43.3%	
	Yes	n	124	189	86	399	
		% in Severity	**37.2%**	**68.5%**	**90.5%**	**56.7%**	0.0001
Glabella	No	n	287	135	16	438	
		% in Severity	86.2%	48.9%	16.8%	62.2%	
	Yes	n	46	141	79	266	
		% in Severity	**13.8%**	**51.1%**	**83.2%**	**37.8%**	0.0001
Nasolabial fold	No	n	321	224	38	583	
		% in Severity	96.4%	81.2%	40.0%	82.8%	
	Yes	n	12	52	57	121	
		% in Severity	**3.6%**	**18.8%**	**60.0%**	**17.2%**	0.0001
Periorbital area	No	n	328	246	61	635	
		% in Severity	98.5%	89.1%	64.2%	90.2%	
	Yes	n	5	30	34	69	
		% in Severity	**1.5%**	**10.9%**	**35.8%**	**9.8%**	0.0001

different clinical features among subtypes and to elucidate the topographical features according to subtype.

The data of the current study show that female predominance was only observed in ETR and combined type. It was quite similar to previous observations which commented the association of male sex with PHY.[9,10] The ETR subtype (55.7%) was the most common and pure PPR subtype (10.4%) was the rarest in our study. However, if we regard combined subtype as PPR following NRSEC classification, then PPR takes the second place (33.0%). These data are compatible with German and Russian studies which reported that PPR subtype was the second most common subtype.[1] In the present study, by subdividing PPR into pure PPR and combined subtypes, we found that the patients with papulopustular eruptions with underlying erythema are twice as common as those with only papulopustular components. PPR subtype was reported to be the most common in Mediterranean region and Latin America.[11-13] The results of our study indicate that the differences in rosacea manifestation among different ethnic groups of more pigmented populations, such as the Far East and Middle East, need to be investigated further. Ethnicity can be one cause of these differences as well as the skin phototype. In this study, about 80% of all patients had components of erythema and telangiectasia if the combined type is included. This result is in agreement with previous reports which have shown the possibility of progression from ETR to another subtype clinically and histopathologically.[3,14] Only two studies have reported on the proportion of patients with both characteristics of ETR and PPR. Both features of rosacea accounted for 25.9% in Caucasian patients with and 51.3% in Asian patients.[3,15] The proportion of combined subtype in our paper was quite similar to that of the study on Caucasian patients in which erythematous components preceded papules or occurred simultaneously in 80% of combined subtype. Based on our research, we could not determine whether combined subtype developed from ETR.

However, as treatment response of PPR and combined type was faster and better than ETR, a longer, more tenacious existence of ETR can be inferred. Perivascular and peri-adnexal infiltrations are universal findings of rosacea regardless of clinical manifestation, although the intensity of inflammation can vary among subtypes.[16] These findings can be an evidence of progression through thesubtypes, and erythematotelangiectatic component can be considered as the initial phase of rosacea.

Despite various clinical and epidemiological reports, the information on topographic differences among subtypes has been insufficient. In this study, glabella and nasolabial fold were significantly more frequently affected in combined type than in ETR, regardless of severity. If we hypothesise that the majority of combined subtype is the progression of ETR, then we can draw the following conclusion: the glabella and nasolabial fold are more prone to be invaded with rosacea progression in all three subtypes. These can be supportive findings for the definitive characteristics of pure PPR. Apart from rhinophyma, the nose was significantly more frequently invaded with higher severity. We found the same tendency in glabella, nasolabial fold and periorbital area. The possible association between nasal rosacea and severity was suggested in a previous study.[17] We suggest new topographical patterns of rosacea which can indicate rosacea severity. In addition to nose, glabella and nasolabial fold involvement could be recognised as an indicator of subtype progression and also of rosacea severity. When we visually examine patients with rosacea, involvement of glabella, nasolabial fold and nose can be an alarming sign of higher severity. Further well-designed studies are necessary to elucidate more precise steps in subtype progression and whether the aforementioned involvement can be a severity index.

The data from this study showed that the excellent response rate of patients with papulopustular eruption (in combined subtype and in PPR) is

significantly higher than that of ETR. Although there was no statistical difference in the response rate between combined subtype and PPR (26.0% vs 41.5%), it is well known that papulopustular component is much more amenable to therapy than erythematotelangiectatic component.[15] From these results we can deduce that patients with solely papulopustular lesions are expected to have a better prognosis than those with an erythematous component. At present, the classification system for subtyping of rosacea is not perfect,[18] and there are ambiguities and grey areas when designating this dynamic spectral disease into one of the four noncontiguous subtypes. From these Korean data, subdividing PPR into pure PPR and combined PPR+ETR may be helpful for therapeutic decision making and for prognostic prediction.

Our study concentrated on the topographic characteristics of rosacea. Seborrheic dermatitis can occur together with rosacea and lesions may overlap topographically. After thorough physical examination and history taking, although a total 16.8% of patients were found to have concurrent seborrheic dermatitis; the topography of rosacea was not affected. There are some limitations in the present study due to its retrospective nature. Because we used clinical photographs for evaluation, the data did not reflect the patients' subjective assessment.

In conclusion, the topographical characteristics of rosacea are distinct according to subtype and severity. In Korean rosacea patients, pure PPR is much less common than the combined subtype, i.e. PPR that progressed from ETR. Glabellar and nasal involvement can be an early marker for subtype transition from ETR to combined subtype. Involvement of nasolabial fold and periorbital area, in addition to the glabella and nose, may be an indicator of severe rosacea. Since the patients who solely have papulopustular eruptions respond well to treatment, we can expect the best prognosis in PPR, followed by combined subtype

and ETR in decreasing order. To understand the exact characteristics of rosacea, an extensive scale prospective survey using well-formulated subtype classification of rosacea is needed.

Conflict of interest

None to declare

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