Dermatology Practical & Conceptual

Clinicopathological Survey of 204 Rosacea Patients Regarding Rosacea Subgroups and Severity

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ABSTRACT

Introduction: Few studies have evaluated the histopathological characteristics of clinical rosacea subtypes in detail.

Objectives: To assess rosacea histopathological features in correspondence to clinical subgroups.

Methods: The histopathological findings of 204 rosacea patients were analyzed retrospectively and were compared among clinical subtypes.

Results: **Thirt-Two Percent** of patients were male and 68% were female. Seventy-three patients had erythematotelangiectatic rosacea (ETR) and 110 had papulopustular rosacea (PPR), 12 were ETR + PPR, 4 ocular, 2 phymatous, and 3 had Morbihan's edema. Perivascular and perifollicular lymphohistiocytic infiltration, perifollicular exocytosis, follicular spongiosis, and ectatic vessels were almost found in all subtypes. Solar elastosis was higher in ETR. Spongiosis, exocytosis of inflammatory cells into epidermis, acanthosis, and granulomatous reaction were higher in PPR. Inflammatory cells exocytosis was more in PPR and phymatous. Demodex folliculorum was identified in 27% of ETR, 33.6% of PPR, 50% of phymatous, one ocular patient, and none of Morbihan edema. Demodex brevis were found in 5% of ETR, 3% of PPR, and 50% of phymatous. Demodex brevis not folliculorum was more in phymatous. Spongiosis was the most common finding in ocular rosacea.

Conclusions: Spongiosis, exocytosis of inflammatory cells, and granulomatous reactions were more in PPR. Solar elastosis was more in ETR. Histopathological findings were compatible with clinical subgroups.

Introduction

Rosacea is a chronic inflammatory skin disorder with a prevalence of approximately 10% [1]. Rosacea is classified into four major subtypes, based on clinical findings: erythematotelangiectatic (ETR), papulopustular (PPR), phymatous rosacea (PHYR), and ocular rosacea (OR) [2,3]. ETR is characterized by varying degrees of facial erythema and telangiectasia. PPR is presented by facial erythema and a variable number of inflammatory papules and pustules. PHYR presents with tissue hypertrophy, skin thickening, and sebaceous gland hypertrophy, and ocular rosacea is presented by nonspecific eye symptoms such as dryness, foreign body sensation, tearing, and itching or signs such as blepharitis, conjunctivitis, chalazion, and hordeolum. The pathogenesis of rosacea is not fully understood but it is believed to be a complex interaction between genetic, immunologic, and neurovascular factors that increase the susceptibility of individuals to environmental triggers such as UV radiation and Demodex [4,5].

Objectives

Few studies are available regarding the clinical and histopathological findings in rosacea. Previous studies demonstrated that although the intensity of inflammation especially perifollicular lymphohistiocytic infiltration was higher in PPR than ETR, there is no specific histological pattern that can be diagnostic for any rosacea subtype [6,7]. The goal of this study was to determine and compare the histopathological findings of rosacea subtypes.

Methods

In this study, the out-patient clinic database was assessed retrospectively and 204 patients diagnosed with rosacea during 2012-2018 that had a biopsy specimen available were enrolled. Rosacea diagnosis was made according to the National Rosacea Society (NRS) Expert Committee based on the clinical findings such as flushing, permanent erythema, papules and pustules, telangiectasia, ocular findings, and phymatous changes. Demographic data were gathered from medical records of our database including sex, age, rosacea subtype, and severity. The four rosacea subtypes were ETR, PPR, PHYR, and OR defined by a modified NRS classification system [2]. The severity was defined based on established criteria. The severity of features such as erythema, papules, and pustules or telangiectasia was scored as absent (grade 0), mild (grade 1), moderate (grade 2), severe (grade 3) [3]. The specimens that were taken from erythematous patches in ETR and papules in PPR were analyzed. If a biopsy was taken from an unknown site (papule or patch not mentioned) the sample was excluded.

We asked one dermatopathologist to determine both epidermal and dermal changes that were present in specimens. Epidermal changes evaluated were parakeratosis, hyperkeratosis, spongiosis, epidermal exocytosis, and interface dermatitis. Dermal changes involved solar elastosis, vascular changes, papillary dermal edema, perivascular or perifollicular inflammatory infiltration, exocytosis of inflammatory cells into hair follicles, follicular spongiosis, and granulomatous reactions. Two main patterns of inflammation were defined as perivascular or perifollicular inflammation. The severity of inflammation was scored between 0 and 3 (0 absence of infiltration; 1, faint infiltration; 2, moderate infiltration; and 3, intense infiltration). The specimens were evaluated in terms of Demodex mite presence. The histopathological findings were compared between subtypes. SPSS version 18 was used to analyze the data statistically. The comparison of certain histopathological findings between rosacea subtypes was made by using the chi-square test or Fisher exact test. Informed consents were obtained from patients.

Results

Clinical Data

The study included 204 rosacea patients with a mean age of 42.5 years. Sixty-five (32%) patients were male and 139 (68%) were female. Seventy-three patients (36%) had ETR, 110 patients (54%) had PPR, 12 patients (6%) had both ETR and PPR, 4 patients had ocular rosacea, 2 of them had PHYR rosacea and 3 patients had Morbihan edema. All rosacea subtypes were more common in females (M/F=1/2) except ocular rosacea which was more seen in males (M/F=3/1) (Table 1) (Figures 1, 2 and 5).

Rosacea Clinical Severity

Regarding the severity of ETR patients, 42.5 % (31/73) had grade 1, 42.5 % (31/73) had grade 2, and 15.06 % (11/73) had grade 3 of the disease. In terms of PPR patients, 21 % (23/110) had grade 1, 62.72 % (69/110) had grade 2, and 16.4% (18/110) had grade 3. In patients with ETR + PPR, 25 % (3/12) had grade 1, 58.3 % (7/12) had grade 2, and 16.7 % (2/12) had grade 3.

Clinicopathological Correlation

The histopathological features of patients based on the three main clinical subtypes are summarized in Table 2.

Spongiosis (N = 82, 42.05%), exocytosis of inflammatory cells (N = 53, 27.17%), acanthosis (N = 36, 18.41%), and parakeratosis (N=27, 13.84%) in the manner of frequencies

Table 1. Distribution of age stratification and sex ratio in all rosacea subtypes.

Rosacea subtype (No)	ETR (73)	PPR (110)	ETR + PPR (12)	PHYR (2)	OR (4)	Morbihanedema (3)	Total
Sex ratio (M/F)	1/3	1/9	1/2	1/1	3/1	1/2	1/2
Age (yrs.)							
<35	28%	33%	32%	50%	50%	67%	32.3%
35-50	34%	40%	38%	0	25%	0	36.3%
>50	38%	27%	30%	50%	125%	33%	31.3%

ETR = erythematotelangiectatic rosacea; OR = ocular rosacea; PPR = papulopustular rosacea; PHYR = phymatous rosacea.

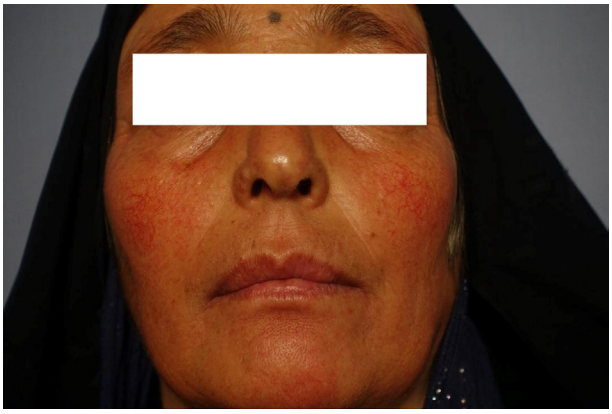

Figure 1. Papulopustular rosacea. Papules, pustules and erythema on the face.

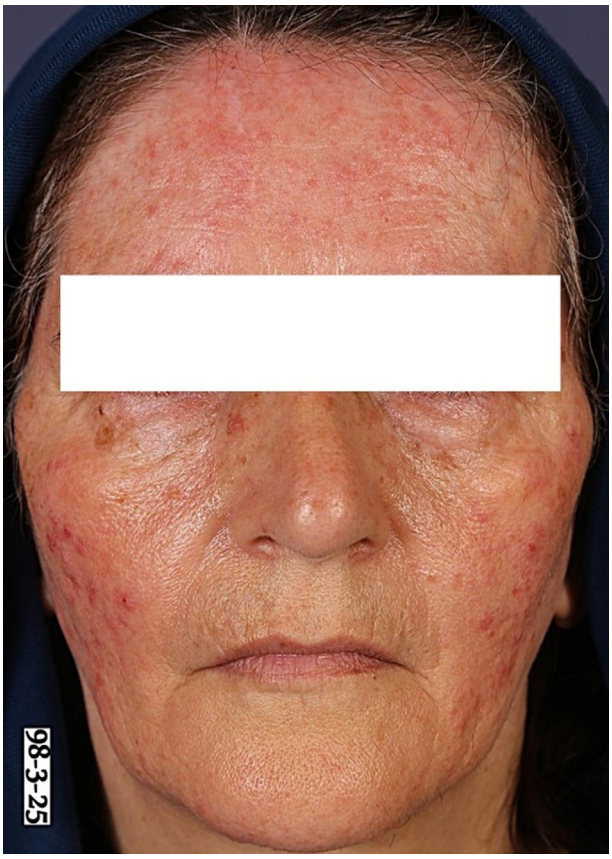

Figure 2. Erythematotelangiectatic rosacea. Persistent erythema and telangiectasia of the cheek.

were the most frequent epidermal changes in the three groups (ETR, PPR, ETR+PPR). Spongiosis (P value = 0.01) was significantly higher in the PPR group than ETR. Interface dermatitis was the least common finding among the 3 subgroups. There was no significant difference between rosacea subtypes in other epidermal changes such as parakeratosis and acanthosis.

The most frequent dermal findings in both groups were ectatic vessels (92% in ETR, 95.5% in PPR), solar elastosis (63% in ETR subtype, 44% in PPR subtype), follicular exocytosis (53% ETR, 61% PPR), and follicular spongiosis (57% ETR and 63% PPR). Both perivascular and perifollicular lymphohistiocytic infiltration were commonly found in ETR and PPR subtypes. Of note, score 1 perivascular infiltration was significantly more common in ETR subtype (42.5%) than PPR (21%) (P value = 0.03), score 2 and 3 of perivascular infiltration though more common in PPR group than ETR but was not statistically significant. Although perifollicular infiltration was commonly found in both subtypes, score 3 of perifollicular lymphohistiocytic infiltration was significantly higher in the PPR subtype (P value = 0.001). Solar elastosis was significantly more common in the ETR than PRP group (P -value = 0.003).

Non-specific granulomatous reactions were significantly more common among PPR patients rather than ETR patients (P value = 0.04). Neutrophilic, eosinophilic, and plasma cell infiltration though more commonly found in PPR than ETR subtype but statistically, no difference was detected. Mast cell infiltration was more common in ETR than PPR but not statistically significant.

Demodex mites were detected in 68 patients comprised of 23 patients with ETR, 39 patients with PPR, 4 with both ETR and PPR, and 2 with ocular rosacea. No correlation between the type of Demodex and histomorphologic findings is identified; *Demodex brevis* but not *folliculorum* was significantly more frequent in phymatous patients (Figure 3). The frequency of two *Demodex brevis* and *Demodex folliculorum* in ETR and PPR subtypes are shown in Table 2. The frequency of Demodex mites showed no difference between groups. The association of Demodex mite frequency and sebaceous hyperplasia, follicular exocytosis, follicular

Table 2. The histopathological features of rosacea patients based on the three main clinical subtypes.

Histopathologic findings	ETR subtype (N=73) N (%)	PPR subtype (N=110) N (%)	ETR + PPR subtype (N=12) N (%)	P value
Epidermal changes				
Parakeratosis	9 (12.3)	17 (15.5)	1 (8.3)	0.58
Hyperkeratosis	2 (2.7)	4 (3.6)	0 (0)	0.12
Spongiosis	24 (33)	56 (51)	2 (17)	0.01
Acanthosis	10 (13.7)	26 (24)	0 (0)	0.14
Exocytosis of inflammatory cells	14 (19.2)	38 (34.5)	1 (8.3)	0.09
Interface dermatitis	0 (0)	2 (1.8)	0 (0)	0.61
Dermal changes				
Papillary dermal edema	12 (16.4)	18 (16.4)	2 (16.7)	0.69
Solar elastosis	46 (63)	48 (44)	9 (75)	0.003
Vascular proliferation or ectatic vessels	67 (92)	105 (95.5)	11 (92)	0.58
Perivascular lymphohistiocytic infiltration				
Score 1 (mild)	31 (42.5)	23 (21)	3 (25)	0.03
Score 2 (moderate)	31 (42.5)	63 (57.3)	7 (59)	0.16
Score 3 (severe)	10 (13.7)	18 (16.4)	2 (16.7)	0.92
Perifollicular lymphohistiocytic infiltration				
Score 1 (mild)	32 (44)	23 (21)	3 (25)	0.22
Score 2 (moderate)	28 (38)	38 (34.5)	6 (50)	0.78
Score 3 (severe)	9 (12.3)	39 (35.5)	2 (16.7)	0.001
Follicular exocytosis	39 (53.4)	6 (61)	8 (67)	0.69
Follicular spongiosis	42 (57.5)	70 (63.6)	8 (66.7)	0.84
Demodex brevis	4 (5.5)	4 (3.6)	0 (0)	0.56
Demodex folliculorum	19 (26)	37 (34)	4 (33)	0.74
Folliculitis	8 (11)	23 (21)	2 (16.7)	0.37
Sebaceous hyperplasia	9 (12.3)	5 (4.5)	1 (8.3)	0.25
Granulomatous reaction	5 (6.8)	27 (24.5)	3 (25)	0.04*
Eosinophil infiltration	13 (17.8)	26 (24)	3 (25)	0.79
Neutrophil infiltration	18 (24.7)	37 (33.6)	3 (25)	0.62
Mast cell infiltration	37 (51)	54 (49)	7 (58.3)	0.59
Plasma cell infiltration	16 (22)	32 (29.1)	2 (16.7)	0.44
Melanin incontinence	10 (13.7)	10 (9.1)	1 (8.3)	0.77

ETR = erythematotelangiectatic rosacea; PPR = papulopustular rosacea.

spongiosis, folliculitis, and deep infiltration was studied. Demodex mite frequency was significantly more common in patients who had follicular spongiosis (Demodex positive 72% versus Demodex negative 57.4%, P value = 0.002), and on the other side follicular exocytosis was negatively associated with Demodex mite presence because, among those patients who had follicular exocytosis, 48.6% were positive for Demodex while 53.7% were negative for Demodex (P value = 0.024) as shown in (Figure 4).

Conclusions

Only a few studies on the histopathological and clinical correlation of rosacea are available [6,7]. In this study, we compared the histopathological findings of rosacea patients according to their clinical subtypes. Histopathological features of various rosacea clinical subtypes are known to be different. The ETR is distinguished mainly by dilated capillaries and venules in the superficial dermis, perivascular and perifollicular lymphohistiocytic infiltration, and solar elastosis. The PPR is characterized by perifollicular lymphohistiocytic infiltration, follicular neutrophilic infiltration, superficial and deep dermal inflammation, and solar elastosis [8].

Our data did not show any histopathological finding specific for clinical rosacea subtypes. Solar elastosis, ectatic vessels, perifollicular and perivascular lymphohistiocytic inflammation were found in all subtypes and not limited to

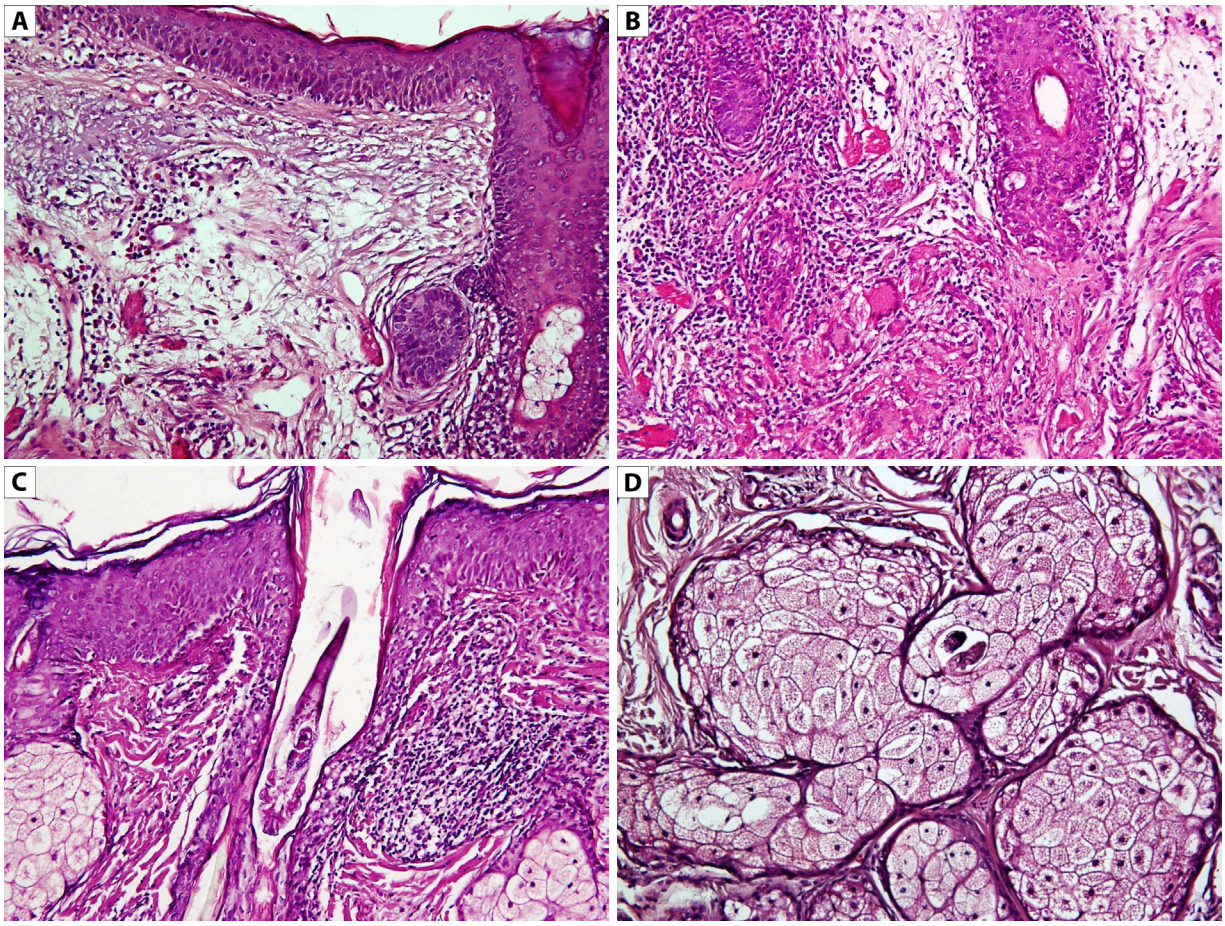

Figure 3. Histopathologic findings. (A) Superficial dermal edema, solar elastosis and moderate perivascular lymphocytic infiltration (H&E × 10 original magnification). (B) Marked perifollicular granulomatous inflammation with lymphohistiocytic cells infiltrate admixed with giant cells (H&E × 10 original magnification). (C) Demodex folliculorum in follicular infundibulum and perifollicular lymphocytic inflammation (H&E × 10 original magnification). (D) Demodex brevis within sebaceous lobules (H&E × 20 original magnification).

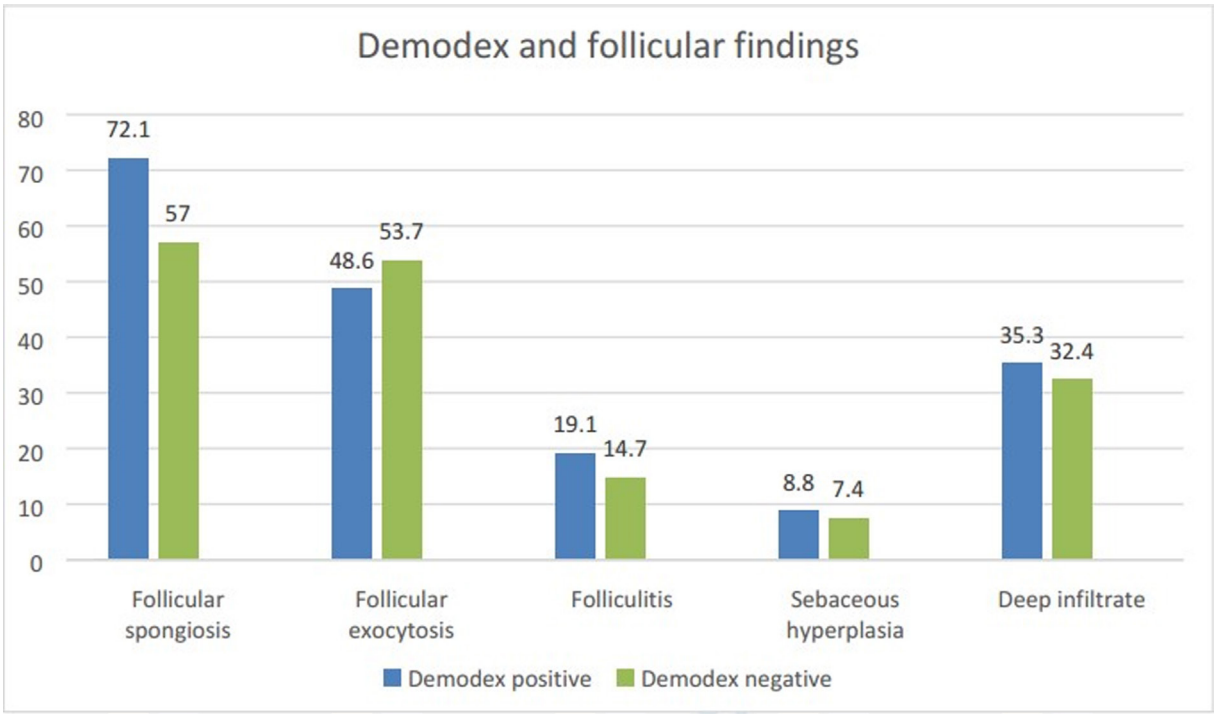

Figure 4. Association of follicular changes and Demodex mite.

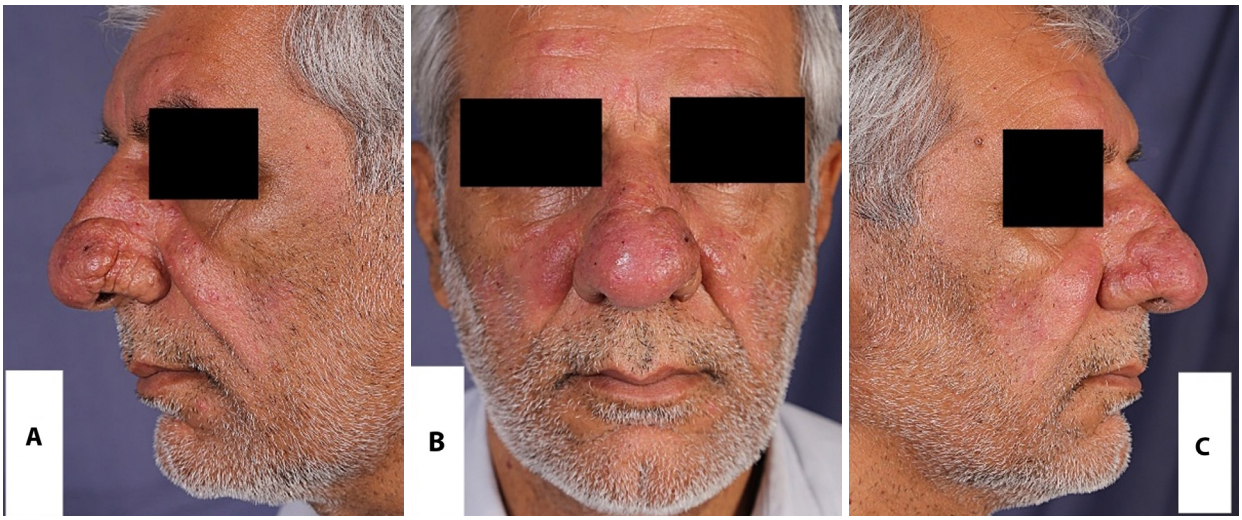

Figure 5. (A-C). Patient with phymatous rosacea.

any subtype. It is believed that follicular inflammation plays a critical role in rosacea pathogenesis [9]. In a previous study perifollicular lymphohistiocytic infiltration was found in 98% of patients with ETR and PPR equally [7]. In our study, the frequency of perifollicular lymphohistiocytic infiltration was 94.5 % in ETR and 73.6 % in PPR with no significant statistical difference. Although grade 3 of perifollicular lymphocytic infiltration was significantly higher in PPR than ETR in our study (P = 0.001), perifollicular infiltration is found in a high proportion of ETR as well and is not specific for PPR. These findings, besides previous studies, suggest that perifollicular lymphohistiocytic infiltration is a nonspecific finding that is found in all rosacea subtypes.

Based on our study, the most frequent epidermal changes in both ETR and PPR subtypes were spongiosis, exocytosis of inflammatory cells, acanthosis, and hyperkeratosis. Previous studies showed that acanthosis, parakeratosis, and exocytosis of inflammatory cells are statistically more common in PPR, which is not supporting the findings of our study. The only epidermal change that was significantly more frequent in PPR than ETR was spongiosis. Previously spongiosis was found in approximately 19% of patients irrespective of the rosacea subtype, but in our study spongiosis was 51% in PPR and 33% in ETR.

Sun exposure is known to play a role in rosacea pathogenesis and the proposed mechanisms are disrupting epidermal barrier function, reduced dermal connective tissue integrity, and reduced dermal vascular support [10,11]. Histopathological markers of sun exposure in rosacea are ectatic vessels in the superficial dermis, solar elastosis, dermal edema, and perivascular inflammation that were all common in both ETR and PPR with no significant difference. Although the presence of enlarged dilated capillaries and venules located in the upper dermis is considered a highly characteristic feature of ETR [8], these findings are commonly seen in PPR too and are not specific to ETR.

Demodex mites were found in a high portion of rosacea patients, the mite was present in more than 75% of rosacea patients in a previous study [12]. It was believed that Demodex mite would play a role in rosacea pathogenesis by inducing perifollicular inflammation. But the recently higher frequency of perifollicular inflammation (more than 90%) in comparison to the lower frequency of Demodex mite, approximately 40% in both ETR and PPR found by Lee et al. led them to the conclusion that pathogenesis of rosacea cannot be only explained by Demodex mite [7]. In our study, the frequency of Demodex mite was 31.5% in ETR and 37.2% in PPR (both Demodex brevis *and* folliculorum) more in support of Lee et al study. Interestingly our study showed that follicular spongiosis is significantly higher in mite positive patients and follicular exocytosis was significantly lower in mite negative patients suggesting that mite may be associated with follicular spongiosis, rather than follicular exocytosis. However, considering current literature, mites are not the only etiologic factor of follicular inflammation and other factors including dysregulated innate immune system and neurogenic dysregulation besides extrinsic factors contribute to the pathogenesis of rosacea [13].

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