

Demodex Mite, Rosacea and Skin Melanoma; Coincidence or Association?

Demodeks Akarı, Rozasea ve Deri Melanomu; Rastlantısal veya İlişkili Birliktelik?

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ABSTRACT

Objective: To examine the possible associations between *Demodex folliculorum* and a number of skin diseases.

Methods: Standardized skin surface biopsy samples were obtained from the cheeks of 144 patients with histopathologically proven basal cell carcinoma (BCC, n=27), squamous cell carcinoma (SCC, n=28), melanoma (n=23), discoid lupus erythematosus (DLE, n=32), and rosacea (n=34). Thirty-four sex- and age-matched healthy volunteers served as controls. Mite density (per cm²) and infestation (density \geq 5) were compared between the controls and patients.

Results: Mite infestation rates (%) did not differ significantly between the controls (20.6) and patients with BCC (22.2, p=0.88), SCC (17.9, p=0.79), melanoma (4.3, p=0.08), and DLE (21.9, p=0.90). Compared with the controls, the mite infestation rate was significantly higher in patients with rosacea (47.1, p=0.02, odds ratio: 3.43, 95% confidence interval: 1.18-9.99). The mean mite density did not differ significantly between the controls (4.11 \pm 2.17) and patients with BCC (5.34 \pm 2.35, p=0.75), SCC (3.57 \pm 2.01, p=0.38), and DLE (3.56 \pm 1.34, p=0.83), whereas it was significantly higher in patients with rosacea (8.78 \pm 3.58, p=0.02) and lower in patients with melanoma (1.89 \pm 0.69, p=0.02).

Conclusions: *D. folliculorum* may be associated with rosacea and melanoma but not with BCC, SCC, or DLE.

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Keywords: Basal cell carcinoma, *Demodex*, discoid lupus erythematosus, melanoma, rosacea, squamous cell carcinoma

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ÖZET

Amaç: *Demodex folliculorum* ve bir dizi deri hastalıkları arasındaki muhtemel bağlantıyı incelemek.

Metot: Standardize yüzeyel deri biyopsisi örnekleri; bazal hücreli karsinom (BCC, n=27), skuamöz hücreli karsinom (SCC, n=28), melanom (n=23), diskoid lupus eritematozus (DLE, n=32), ve rozasea (n=34) tanıları histopatolojik olarak kanıtlanmış 144 hastanın yanaklarından alındı. Cinsiyet ve yaşı eşleştirilmiş 34 sağlıklı gönüllü kontrol grubunu oluşturdu. Akar dansitesi (cm² başına) ve enfestasyon (dansite \geq 5) hasta ve kontrol grubu arasında karşılaştırıldı.

Bulgular: Akar enfestasyon hızları (%) kontrol grubu (20,6) ile BCC (22,2, p=0,88), SCC (17,9, p=0,79), melanom (4,3, p=0,08), ve DLE (21,9, p=0,90) hastaları arasında anlamlı bir farklılık göstermedi. Kontrol grubuna kıyasla, akar enfestasyon hızı, rozasea olanlarda anlamlı olarak yüksekti (47,1, p=0,02; odds oranı: 3,43, %95 güven aralığı: 1,18-9,99). Ortalama akar dansitesi kontrol grubu (4,11 \pm 2,17) ile BCC (5,34 \pm 2,35, p=0,75), SCC (3,57 \pm 2,01, p=0,38), ve DLE (3,56 \pm 1,34, p=0,83) hasta grupları arasında anlamlı bir fark göstermezken, kontrol grubuna kıyasla

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rozasea hastalarında ($8,78 \pm 3,58$, $p=0,02$) anlamlı olarak daha yüksekti ve melanom hastalarında ($1,89 \pm 0,69$, $p=0,02$) anlamlı olarak daha düşüktü.

Sonuç: *Demodex folliculorum*, rozasea ve melanom ile ilişkili olabilir, ancak BCC, SCC ve DLE ile ilişkilendirilemez. (Turkiye Parazitoloj Derg 2015; 39: 41-6)

Anahtar Sözcükler: Bazal hücreli karsinom, *Demodex*, diskoid lupus eritematozus, melanom, rozasea, skuamöz hücreli karsinom

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INTRODUCTION

The human hair follicle mites *Demodex folliculorum* and *D. brevis* are obligatory commensals of the pilosebaceous unit and the most prevalent ectoparasites (1)

Despite their high existence rates, these mites usually do not cause symptoms unless their density is abnormally increased on the skin (i.e., >5 mites per cm^2) (2). More importantly, some studies have proposed causative/exacerbating roles for *Demodex* mites in the pathogenesis of several benign and malignant skin diseases such as rosacea (3), pityriasis (4), skin bacterial infections (5), dermatitis (6) acne vulgaris (7), basal cell carcinoma (BCC), and squamous cell carcinoma (SCC) (8, 9).

Although the exact underlying mechanisms of such associations between particular skin diseases and *Demodex* mites are yet to be elucidated, several hypotheses have been suggested: (i) provocation of inflammatory and immune reactions, (ii) role of *Demodex* mites as a vector for other pathogens, and (iii) mechanical obstruction of the follicles (10)

Because of these uncertainties and considering the clinical and therapeutic implications of a probable association between *Demodex* mites and some skin diseases, further investigations are necessary. Well-designed, case-controlled studies, in particular, are essential to rule out a possibility of a mere coincidence of skin diseases and *Demodex* infestation (11).

Thus, the present study sought to examine a possible association of *D. folliculorum* density and its infestation rate with some malignant (i.e., BCC, SCC, and melanoma) and non-malignant [i.e., discoid lupus erythematosus (DLE) and rosacea] skin diseases.

METHODS

Study population

After approval by the ethics committee of the Tabriz University of Medical Sciences, a total of 144 patients with histopathologically proven BCC ($n=27$), SCC ($n=28$), melanoma ($n=23$), DLE ($n=32$), and inflammatory (papulopustular) rosacea ($n=34$) were recruited from 3 dermatopathology teaching centers from October 2008 through July 2014.

The principal lesions in patients with BCC, SCC, and melanoma were located on the cheeks. In patients with DLE and rosacea, the cheeks were clinically involved.

A series of healthy age- and sex-matched volunteers ($n=34$) with no dermatological disease or telangiectasia served as controls.

Patients with a history of receiving any topical and/or systemic antibiotic, acaricides, and corticosteroid/immunosuppressive within a month prior to enrolment and those who underwent radiotherapy and/or chemotherapy before skin samplings were not included.

Informed written consents were obtained from all participants.

Procedure

The presence of *D. folliculorum* was investigated by a non-invasive technique, known as standardized skin surface biopsy (SSSB). For this, a drop of cyanoacrylate glue (approximately 0.05 mL) was placed on a 1- cm^2 area marked on a slide glass surface by a waterproof pen.

The adhesive-containing side was pressed against the cheek skin for approximately 1 min and then peeled off gently. Cover slips were placed on the sample covered by 2 drops of immersion oil; the specimens thus prepared were examined immediately under light microscopy ($\times 40$ and $\times 100$ magnification) by a skilled dermatopathologist (with over 10 years of experience) blind to the groupings.

In the groups including patients with BCC, SCC, and melanoma, the samplings were performed from the skin adjacent to the lesions and the symmetrical spots of the contralateral (uninvolved) cheek.

In the groups including patients with DLE and rosacea, the samplings were performed from both cheeks. In order to perform between-group comparisons, the results acquired from the right cheeks were arbitrarily employed.

The skin and the slides were cleansed with ether prior to the samplings (12).

Cheek *Demodex* density was reported as the number of mites per cm^2 of the skin (6, 13). Infestation was considered positive when the mite density was ≥ 5 per cm^2 (14).

Statistical analysis

SPSS software version 16.0 (SPSS Inc., IL, USA) was used for statistical analysis. One-way analysis of variance (ANOVA), Tukey's post-hoc test, independent samples *t* test, and chi-square test were used for comparisons where appropriate. A *p*-value of ≤ 0.05 was considered statistically significant.

RESULTS

The demographic information of the study groups, including sex and age, is presented in Table 1.

No significant differences were present between the groups of patients and healthy controls in terms of sex and age ($p > 0.05$ for all comparisons).

Cheek mite infestation was positive in 7 healthy controls (20.6%), 6 patients with BCC (22.2%), 5 patients with SCC (17.9%), 1 patient with melanoma (4.3%), 7 patients with DLE (21.9%), and 16 patients with rosacea (47.1%) (Figure 1).

In comparison with the controls, no significant differences were found in terms of cheek mite infestation rates in the BCC [$p=0.88$, odds ratio (OR)=1.10, 95% confidence interval (CI): 0.32-3.77], SCC ($p=0.79$, OR=0.84, 95% CI: 0.22-3.00), melanoma

Table 1. Demographic information of the study groups

Study groups (n)	Age (year)	Sex		p-value ^a	p-value ^b
		Male	Female		
Basal cell carcinoma (27)	65.21±13.12	16 (59.3)	11 (40.7)	0.69	0.62
Squamous cell carcinoma (28)	64.09±13.22	19 (67.9)	9 (32.1)	0.59	0.23
Melanoma (23)	66.38±12.59	12 (52.2)	11 (47.8)	0.13	0.96
Discoid lupus erythematosus (32)	61.44±18.14	16 (50)	16 (50)	0.27	0.81
Rosacea (34)	60.09±20.20	16 (47.1)	18 (52.9)	0.52	0.63
Control (34)	64.24±19.45	18 (52.9)	16 (47.1)	-	-

Data are presented as mean±standard deviation or frequency (%).
^aAge of patients vs. age of controls
^bSex of patients vs. sex of controls
^{*}p≤0.05 is considered statistically significant.

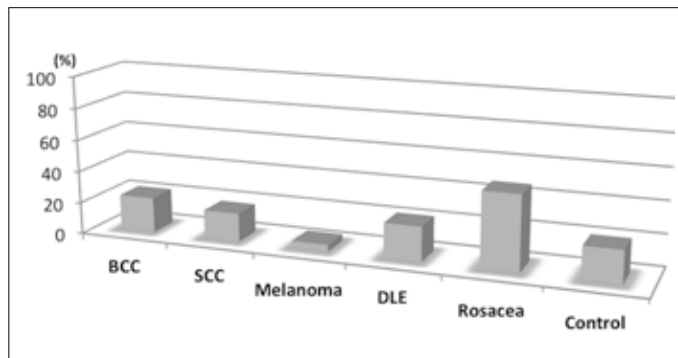


Figure 1. Cheek mite infestation rates in the study groups
 BCC: basal cell carcinoma, DLE: discoid lupus erythematosus, SCC: squamous cell carcinoma

(p=0.08, OR=0.18, 95% CI: 0.02-1.54), or DLE (p=0.90, OR=1.10, 95% CI: 0.33-3.52) groups.

The rate of cheek mite infestation, however, was significantly higher in the rosacea group compared with the controls (p=0.02, OR=3.43, 95% CI: 1.18-9.99).

The mean cheek mite densities in the study groups are summarized in Table 2.

No significant differences were documented when the 2 sides in each group were compared with each other.

Statistically significant differences were found between the study groups concerning the mean cheek mite densities on the involved (for the BCC, SCC, and melanoma groups) or right (for the DLE, rosacea, and control groups) sides (p=0.03).

According to the results of post-hoc analysis, statistically significant differences were present between the control and melanoma groups (p=0.02) as well as between the control and rosacea groups (p=0.02).

DISCUSSION

We found that both mite density and infestation rate were associated with rosacea in the present study. This finding is in line with that of previous reports (15-21).

It has been postulated that increased mite number in cases with abnormally elevated mite density may lead to the obstruction of the hair follicles and plugging of the sebaceous ducts. In addition, presence of mites on the skin may damage the follicular epithelia directly or indirectly through the induction of hypersensitivity reactions. Co-infections with *Staphylococcus albus* and *Bacillus oleronius* are frequently seen in patients with rosacea, and *Demodex* mite infestation has raised a concern regarding the role of these mites as a vector for the bacteria. The exact mechanism underlying the connection between rosacea and *Demodex* mites, however, is not identified (22-24).

It should be noted that the patients with rosacea examined in the present study were affected only with the papulopustular subtype of the disease. In a previous study, however, it was concluded that a probable pathological role of *Demodex* mites in rosacea is independent of the disease subtype (25).

In another part of this study, we did not find a significant association of mite density or infestation rate with DLE. Similar findings were reported in another study by Perrigouard et al. (26) who detected no mites on the skin of patients with lupus erythematosus. In another series, Moravvej et al. (27) reported *Demodex spp.* on the skin of 38.6% of patients with rosacea and only 21.3% of patients with DLE. Both reported values are close to those found in the present study. In conformity with our results, Roihu et al. (28) also reported no significant difference in mite counts of infested follicles between patients with DLE and healthy referents.

Unlike benign skin disorders such as rosacea and DLE, available data in the literature concerning the association between *Demodex* mites and malignant skin conditions are conflicting. In a study on Turkish patients, Erbagci et al. (9) reported a higher infestation rate and mean density of *Demodex* mites in patients with BCC compared with that in a healthy sex- and age-matched group. In another series by Sun et al. (8), facial skin specimens were obtained from patients with BCC and SCC and non-malignant skin disease. They found that the rate of mite infestation was significantly higher in patients with BCC and lower in patients with SCC compared with that in patients with non-malignant conditions. In contrast to these studies, we did not observe significant associations between SCC/BCC and *D. follic-*

Table 2. Cheek mite densities in the study groups

Study groups (n)	Side	Mite density (per cm ²)	p-value ^a	p-value ^b
Basal cell carcinoma (27)	Affected	5.34±2.35	0.75	0.89
	Unaffected	5.01±2.12		
Squamous cell carcinoma (28)	Affected	3.57±2.01	0.38	0.79
	Unaffected	4.56±2.36		
Melanoma (23)	Affected	1.89±0.69	0.02*	0.63
	Unaffected	1.17±0.35		
Discoid lupus erythematosus (32)	Right	3.56±1.34	0.83	0.83
	Left	3.90±1.29		
Rosacea (34)	Right	8.78±3.58	0.02*	0.91
	Left	8.18±3.12		
Control (34)	Right	4.11±2.17	-	0.92
	Left	4.01±2.23		

Data are presented as mean±standard error of the mean
^aPatients vs. controls
^bAffected side vs. unaffected side or right side vs. left side
 *p≤0.05 is considered statistically significant.

lorum. This heterogeneity between reports may arise from methodological flaws and varying characteristics of the study populations. Missing well-selected control groups; different time, sites, and methods of sampling; and employment of inappropriate techniques for detecting mites and calculating their density are possible confounding factors.

Some studies have suggested a direct, significant correlation between the likelihood of mite infestation and age (29, 30). All our patient groups were comparable with the controls in terms of age.

Although no significant associations have been shown between mite infestation and host gender, skin type, hygiene, and use of cosmetics (31) we did our best to select patients and healthy referents with the highest similarities for these factors.

Because an incompetent immune system has been suggested as a potential risk factor for pathological mite infestations (32, 33), we performed all samplings prior to the commencement of any treatment to ensure that the patients' immune system was unaffected. In addition, all samplings in the present study were performed on the cheek skin, because the highest density of mites has been reported to be on this facial area (34).

There are various skin sampling methods in order to examine *Demodex* mites. Using adhesive tapes, comedo extraction, hair epilation, skin impression/scraping, skin biopsy, and skin surface biopsy are the most commonly used techniques in this regard (13, 14, 34). We chose the SSSB technique owing to its non-invasiveness and high sensitivity compared with the other available methods (12, 35).

Although statistically insignificant, the rate of mite infestation was clearly lower in specimens obtained from patients with melanoma in comparison with those obtained from the controls

(4.3% vs. 20.6%; p=0.08). Significantly lower mean mite density in patients with melanoma compared with that in the controls further corroborated a possible association between *D. folliculorum* and melanoma. To the best of our knowledge, this is the first study in the literature that reports such an association. Although the results need to be clarified in future studies, this finding may suggest a shared point in human immunological host defense against both melanoma and *Demodex* mites (36-38). Although challenging in its essence, another relevant hypothesis may be a protective role of mites against melanoma or vice versa.

In the present study, no significant differences were found between the 2 cheeks in each group in terms of mite infestation rates, a finding in line with that of a previous report indicating symmetrical facial mite distribution in healthy individuals (35). It is not known whether this symmetry represents a systemic rather than local phenomenon in connecting skin disease and *Demodex* mites.

CONCLUSION

According to the findings of the present study, there may be no association between *D. folliculorum* and BCC, SCC, and DLE. In conformity with available data, both *Demodex* mite density and infestation rate could be associated with rosacea. An inverse association was observed between *D. folliculorum* and melanoma, which merits investigation in future, multi-center studies.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Tabriz University of Medical Sciences.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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