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Abstract

Background: Acne rosacea (AR) is a chronic inflammatory skin disease that can cause serious ocular complications.

Objectives: We aimed to evaluate dry eye disease (DED), meibomian gland dysfunction (MGD) in AR patients with meibography, to investigate the relationship between cutaneous subtypes and ocular involvement.

Methods: This study included 67 participants with AR, 50 healthy individuals. The patients were classified into the following three cutaneous subtypes: erythematotelangiectatic rosacea (ETR), papulopustular rosacea (PPR), phymatous rosacea (PR), and referred for ophthalmatological examination including; meibomian gland obstruction lid margin alterations assessment, Ocular Surface Disease Index assessment, tear film break-up time test, Schirmer test, corneal conjunctival fluorescein staining assessment. Upper and lower lids were evaluated for meibomian gland loss with meibography.

Results: MGD (45.5%) and DED (28.1%) were found in AR group. Meibomian gland loss rate (MGLR) was 38.7 ± 16.9 and Meibomian gland loss grade (MGLG) was 1.57 ± 0.82. MGLR and MGLG were significantly higher in the AR group compared with the control group (p<0.001). 59.7% of 67 patients consisted of PPR, 29.9% of 67 patients consisted of ETR, and 13.4% of 67 patients consisted of PR. When we compared three groups with each other in terms of MGD, MGLR, MGLG, DED, the results were interpreted as statistically insignificant.

Conclusions: AR can cause structural changes by affecting meibomian gland morphology, as a result of these may cause MGD and DED. Therefore, ophthalmologists and dermatologists should co-evaluate the patients in this respect.

Key Words: Dry eye disease, Meibography, Meibomian gland dysfunction, Ocular surface diseases, rosacea

Introduction

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Acne rosacea (AR) is a common, chronic, inflammatory skin disorder that is characterized by redness, inflammatory papules and plaques, telangiectases, and phyma on the mid-facial areas including cheeks, nose, chin, and forehead with multifactorial causes. The disease has relapsing and remitting periods. Some trigger factors such as exposure to heat, spicy foods, or ultraviolet radiation may cause flare-ups in patients with AR (1,2). Based on specific clinical findings, AR was classified into the following four subtypes: erythematotelangiectatic rosacea (ETR); papulopustular rosacea (PPR); phymatous rosacea (PR); and ocular rosacea (OR) (3).

According to previous studies in the literature, the incidence of ocular involvement in AR is claimed to be from 6% to 72% (4). The studies from the literature showed that most of the ocular involvement was in the form of ocular surface abnormalities and impaired tear function. Ocular rosacea often includes meibomian gland dysfunction (MGD), chronic conjunctivitis, and recurrent chalazions.

MGD is an ocular disease in which terminal duct obstruction and quantitative-qualitative changes in secretions are seen clinicopathologically (5). The prevalence of MGD ranges from 3.5% to 74.5% (6-8). Plugging of MG, Meibomian secretions, telangiectasia, gland loss, as well as a combination of some of these parameters have been used to diagnose MGD (7,8). A significant relationship has been found between AR and MGD in studies; and meibography, which is a noninvasive current objective approach and has now been widely preferred for clinical use, has been used in the studies with AR (9).

Although this disease can have a considerably negative psychosocial effect on patients and may be cause blinding if left untreated, OR is frequently overlooked by clinicians, both dermatologists and ophthalmologists. This study differs from other studies about AR from the literature in terms of comparing ocular involvement with cutaneous subtypes with current technique meibography.

In this study, we aimed to evaluate the relationship between dry eye disease (DED) and MGD which are the most common manifestations of OR with cutaneous subtypes of AR.

Materials and Methods
This single-center, case control cross-sectional study was carried out in Aksaray University Research and Training Hospital after receiving Institutional Review Board protocol approval (dated 19.04.2019; number 2019/03-60 from the local committee of Clinical and Laboratory Research Ethics in Aksaray University). Sixty-seven patients aged 18 to 65 years, and clinically diagnosed as AR by the same dermatologist with standard diagnostic criteria (10) admitted to dermatology outpatient clinic between June and August 2019, and 50 healthy control individuals were enrolled. Patients with other inflammatory skin diseases, autoimmune diseases, other systemic diseases that can cause ocular involvement and, drug users were excluded. Additionally, participants with ocular infection, allergy, ocular surface disorder, who had anamnesis of eye surgery or trauma, who have been under topical or systemic treatment which can affect the ocular surface, and users of contact lens were excluded from our study.

**Diagnosis and assessment of acne rosacea**

All subjects were examined by the same dermatologist. Demographic features of the participants were recorded. The patients were classified into the following three cutaneous subtypes: erythematotelangiectatic rosacea (ETR), papulopustular rosacea (PPR), phymatous rosacea (PR) (3).

**Diagnosis and assessment of eye disease**

Examination and tests were performed as follows: Upper and lower eyelids were evaluated with a microscope for obstruction, telangiectasia, notching, and mucocutaneous junction shift. After the examination, fluorescent staining of the ocular surface, tear break-up time (TFBUT) test, Schirmer test and meibography test were done.

The diagnosis of MGD was made according to the diagnostic criteria recommended by the MGD Study Group in Japan (6). MGD was diagnosed when the meibomian gland (MG) was occluded and there were lid margin abnormalities. For Meibography testing, the BG-4M Non-Contact System was used throughout the study (Sirius, Costruzione Strumenti Ophthalmici, Firenze, Italy). MG examination was performed with a slit lamp and infrared imaging of a video camera. The rate of MGL area to the total area of the glands was calculated by using the

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software and the examiner marked the total area and loss of area, and the percentage of the MGL were calculated. MGL was categorised as grade 0 (no loss of MG), grade 1 (0-1/3 of the total MG), grade 2 (1/3-2/3 of the total MG), and grade 3 (>2/3 of the total MG) (11). Grading of MGL was performed blindly by the same researcher. MG distortion was classified as 0 (<50% of the changes) or 1 (>50% of the changes). The meiboscores and MG distortion for the lower-upper eyelids were evaluated for the right eye.

The DED was diagnosed using the modified Tear Film & Ocular Surface Society Dry Eye Workshop II (TFOS DEWS II) Criteria: Ocular Surface Disease Index (OSDI) > 13 plus one among TFBUT < 10 s, Schirmer test score < 10 mm, or conjunctival and corneal staining > 0 (12) TFBUT, Schirmer test, and conjunctival and corneal staining were done on the right eyes.

**Statistical Analysis**

The results were subjected to statistical analysis on, “Statistical Package for Social Science for Windows (SPSS v23)”. The Shapiro–Wilk test was used to evaluate whether the distribution of the numerical data was normal.

The independent sample t-test was used to compare the means of numerical variables between the two groups. The chi-square test was used to compare the means of categorical variables between the two groups. Binary logistic regression analyses were applied to compute odds ratios for the associations between the explanatory variables. A p-value less than 0.05 was considered statistically significant.

**Results**

Sixty-seven patients were enrolled who were diagnosed with AR in this study, including 43 (64.2%) females and 24 (35.8%) males. The mean patient age was 41.31 ± 12.63 years. In the control group, 40% (n= 20) of the participants were male, while 60% (n=30) were female. The mean age in the control group was 40.21 ± 8.85 years. There were no significant differences between patient and control groups in terms of age, and gender (p>0.05). Demographic features of the participants were presented in Table 1.
According to the clinical anamnesis of the patients, 16 of 67 patients (23.8 %) had subjective ocular symptoms, such as itch, burning, and stinging. The frequency of MGD was 45.5% (n=30) in the rosacea group, and 11.5% (n=6) in the control group (p<0.001). A statistically significant difference was found between rosacea and control groups according to Meibomian Gland Loss Rate (MGLR), and Meibomian Gland Loss Grade (MGLG) (p<0.001) (Table 2). The frequency of DED in the rosacea group was 28.1% (n=18), whereas it was 5.8% (n=3) in the control group (p=0.044) (Table 2). The relationship between MGD and age, gender, duration of AR, and cutaneous subtypes of AR was assessed with a binomial logistic regression test. No significant relationship was observed between MGD and age, gender, duration of AR, cutaneous subtypes of AR (p > 0.05) (Table 3). The relationship between DED and age, gender, duration of AR, and cutaneous subtypes of AR was evaluated with a binomial logistic regression test. A significant relationship was found between DED and age (p=0.038). No significant relationship was observed between DED and gender, duration of AR, cutaneous subtypes of AR (p > 0.05) (Table 4). 59.7% of 67 patients consisted of PPR, 29.9% of 67 patients consisted of ETR, and 13.4% of 67 patients consisted of PR. When we compared three groups with each other in terms of MGD, MGLR, MGLG, and DED, insignificant difference was observed between PPR, ETR, PR groups (p > 0.05) (Table 5).

Discussion

The prevalence of AR is estimated to reach over 5% worldwide. Females and males are equally affected (13). Ocular rosacea which is assessed as one of the discrete subtypes of AR in the classification of National Rosacea Society is a common condition that can be blinding if inadequately treated (3). This condition is usually overlooked by clinicians. Ocular rosacea may occur independently from cutaneous findings in about one-third of cases (14,15). The severity of cutaneous findings...
has not been related to ocular involvement. It has been suggested that ocular involvement is more likely to be seen with ETR and PPR which are cutaneous subtypes of AR, it is estimated that the risk of ocular inflammation is about 50% in these cutaneous subtypes (16).

Most of the ocular involvement was in the form of ocular surface abnormalities and impaired tear function. Marginal corneal infiltrates, ulceration, corneal neovascularization and scarring, scleral perforation, episcleritis, scleritis, and iritis have also been reported in studies (4).

MGD is one of the most chronic ocular disorders in OR. In 90% of patients with ocular rosacea, eyelid changes including MGD are seen (17). Pathophysiology is explained by the immunological mechanism in which type 4 hypersensitivity reaction is predominant. An unknown antigen such as *staphylococcus aureus, staphylococcus epidermidis, Demodex follicularum* reaches the globe with tears from diseased valves, and secretion is disrupted in MG by mediators released from inflammatory cells (18).

MG are sebaceous glands which take place at the edges of eyelids. The secretions of the glands provide evaporation of water from the tears due to the lipids in their content, ensuring that the ocular surface is well-lubricated and healthy. MGD is an ocular disease in which terminal duct obstruction and quantitative-qualitative changes in secretions are seen clinicopathologically (5). These result in changes in tear structure and, cause clinical signs of ocular irritation (19).

In the study as mentioned above, it was observed that male sex, age, and the use of lipid-lowering agents were significantly associated with MGD, whereas female sex, contact lens wear, and the presence of conjunctivochalasis or lid margin abnormalities were significantly associated with DED (20). In current study, it was found that MGD was not significantly associated with age and, gender. However, DED was a significantly associated with age, whereas no association was observed between DED and gender. The differences may be due to the difference of the sample size.
AR can trigger MGD and DED (21). In our study, the incidence of MGD and DED was found high in patients with AR as previous similar studies in the literature. Additionally, it was observed that ocular disease (both MGD and DED) was not significantly associated with duration of AR and, cutaneous subtypes of AR.

Zengin et al. reported a significant decrease in tear function tests (Schirmer and tear break-up time tests) with an increase in MGD in patients with OR as the results of our study (22). In a study by Evren et al., the signs of DED, lid margin telangiectasia, metaplasia in the Meibomian gland orifices were significantly higher found in 21 patients with AR (8 took oral doxycycline, 13 did not) compared to the control group. Lower tear film meniscus height, and Meibomian gland secretion quality were observed when compared to controls. However, no significant difference was observed between patients with AR who received treatment and those who did not. In lipid analysis, a significant difference was found between the untreated group, the treated group, and the control group (23). Sobrin et al. reported an increase in matrix metalloproteinase-9 (MMP-9), tissue inhibitor of metalloproteinase-1 (TIMP-1), and interleukin-1 levels in the tears of patients with AR (24). A study was reported that high oleic acid levels in both meibum triglycerides and free fatty acids in meibomitis patients diagnosed with AR, and they stated that the presence of high oleic acid could be controlled with minocycline treatment (25).

In a retrospective descriptive study of Akpek et al. with 131 OR patients, it was found cutaneous findings in 112 patients. However, the relationship between OR and cutaneous subtypes was not evaluated in detail (26).

In a case study of 176 AR patients, 88 were from dermatology clinics and 88 were from ophthalmology clinics, evaluating the prevalence of AR, 25% of patients in dermatology clinics had ocular symptoms. MGD, telangiectasia, interpalpebral conjunctival hyperemia, and anterior blepharitis were found statistically significantly higher in patients from ophthalmology clinics compared to patients from dermatology clinics. There was no significant difference according to corneal, episcleral, and lens findings between patients from two clinics (15). In a study by Machalińska et al., 41 AR patients and 44 controls were evaluated using meibography,
and it is reported that cutaneous rosacea is associated with ocular erythema and lid margin abnormalities. They compared cutaneous subgroups with each other in terms of only lid margin abnormality scores, they found statistically significant difference. They suggest that ocular signs of rosacea may affect on meibomian gland morphology, causing MGL and OR is associated with the loss of Meibomian gland tissue (27). Palamar et al evaluated 18 patients with AR and compared them with 19 controls using meibography. They did not divide the patients into cutaneous groups, unlike our study. They suggest that OR causes DED and significant MGL that can objectively be demonstrated with meibography (10).

There are studies in the literature comparing cutaneous subtypes of AR in terms of disease severity, progression, and histopathological features (28,29). However, no study was found that evaluated the relationship between OR and cutaneous subtypes of AR in detail.

According to the results of the study, the incidence of MGD and DED was found high in AR as previous similar studies in the literature. We suggest that AR can cause structural changes by affecting meibomian gland morphology, and as a result of these may cause MGD and DED.

We did not observe a remarkable relationship between cutaneous subgroups and ocular findings (MGD, MGLR, MGLG, DED).

Meibography is a current objective method, a noninvasive approach which has been widely preferred by clinicians for patients with meibomian gland diseases, and it has allowed many studies about MGD to be carried out. In the literature, only two studies evaluated the AR patients using meibography as our study (10,26).

Smaller study groups and the inability to detect quality changes of meibum with meibography were limitations of the study.

Conclusion

We emphasize that possible serious ocular complications can be preventable with early diagnosis and treatment by evaluating carefully together as dermatologists and ophthalmologists in terms of clinical findings of MGD and DED. On the other hand, the dermatological literature has generally not adequately pointed these complications; however, a
thorough understanding and management of ophthalmic involvement are important for the comprehensive care of patients with AR. We underline that ocular involvement is very common in patients with AR. Therefore, dermatologists and ophthalmologists should be aware of MGD and DED which may accompany patients with AR. In this study, 16 of 50 patients (23.8%) had ocular symptoms. Therefore, we think that periodic ophthalmological examinations should be performed in patients with AR regardless of the presence of ocular symptoms, and early diagnosis of the condition gives patients the chance of treatment, improves the patients’ quality of the life. Although we found no difference between cutaneous subtypes in terms of MGD and DED, we think that further researches should be performed with the larger study groups to assess the relationship between cutaneous subgroups and ocular involvement, and achieve more assuring results.

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4- Ozek D, Kemer ÖE, Artüz F. Assessment of Tear Functions in Patients with Acne Rosacea without Meibomian Gland Dysfunction. Ocular Immunology & Inflammation, 2019; 27(4): 632–635

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Legends of Tables

Table 1. Demographic features of participants

Table 2. Comparison of rosacea and control groups in terms of ocular involvement

Table 3. The relationship between MGD and age, gender, duration of rosacea, and cutaneous subtypes of rosacea

Table 4. The relationship between DED and age, gender, duration of rosacea, and cutaneous subtypes of rosacea

Table 5. Comparison of rosacea cutaneous subtypes and controls in terms of ocular involvement
Table 2. Comparison of rosacea and control groups in terms of ocular involvement

<table>
<thead>
<tr>
<th></th>
<th>Rosacea Group</th>
<th>Control Group</th>
<th>p</th>
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</thead>
<tbody>
<tr>
<td>MGD n (%)</td>
<td>30 (45.5)</td>
<td>6 (11.5)</td>
<td>p&lt;0.001</td>
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<tr>
<td>MGLR</td>
<td>38.7 ± 16.9</td>
<td>12.9 ± 11.3</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>MGLG</td>
<td>1.57 ± 0.82</td>
<td>0.40 ± 0.57</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>DED n (%)</td>
<td>18 (28.1)</td>
<td>3 (5.8)</td>
<td>p=0.004</td>
</tr>
</tbody>
</table>

MGD: Meibomian Gland Dysfunction; MGLR: Meibomian Gland Loss Rate; MGLG: Meibomian Gland Loss Grade; DED: Dry Eye Disease

Tablo 3. The relationship between MGD and age, gender, duration of rosacea, and cutaneous subtypes of rosacea

<table>
<thead>
<tr>
<th></th>
<th>Sig.</th>
<th>Odds Ratio</th>
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<tr>
<td>ETR</td>
<td>.406</td>
<td>.448</td>
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<tr>
<td>PPR</td>
<td>.500</td>
<td>.538</td>
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<tr>
<td>PR</td>
<td>.675</td>
<td>.697</td>
</tr>
<tr>
<td>Duration</td>
<td>.979</td>
<td>1.001</td>
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<tr>
<td>Age</td>
<td>.339</td>
<td>1.022</td>
</tr>
<tr>
<td>Gender</td>
<td>.295</td>
<td>1.909</td>
</tr>
</tbody>
</table>

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### Tablo 4. The relationship between DED and age, gender, duration of rosacea, and cutaneous subtypes of rosacea

<table>
<thead>
<tr>
<th></th>
<th>Sig.</th>
<th>Odds Ratio</th>
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<td>ETR</td>
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<td>.338</td>
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<tr>
<td>PPR</td>
<td>.420</td>
<td>.372</td>
</tr>
<tr>
<td>PR</td>
<td>.613</td>
<td>.685</td>
</tr>
<tr>
<td>Duration</td>
<td>.376</td>
<td>.933</td>
</tr>
<tr>
<td>Age</td>
<td>.038</td>
<td>1.535</td>
</tr>
</tbody>
</table>

ETR: Erythematotelangiectatic Rosacea; PPR: Papulopustular Rosacea; PR: Phymatous rosacea

MGD: Meibomian Gland Dysfunction
Table 5. Comparison of rosacea cutaneous subtypes and controls in terms of ocular involvement

<table>
<thead>
<tr>
<th></th>
<th>ETR (n (%)</th>
<th>PPR (n (%)</th>
<th>PR (n (%)</th>
<th>Controls (n (%))</th>
</tr>
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<tbody>
<tr>
<td>GENDER</td>
<td>.461</td>
<td>.572</td>
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<tr>
<td>ETR: Erythematotelangiectatic Rosacea; PPR: Papulopustular Rosacea; PR: Phymatous rosacea; DED: Dry Eye Disease</td>
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<table>
<thead>
<tr>
<th></th>
<th>ETR</th>
<th>PPR</th>
<th>PR</th>
</tr>
</thead>
<tbody>
<tr>
<td>MGD</td>
<td>10</td>
<td>18</td>
<td>3</td>
</tr>
<tr>
<td>MGLR</td>
<td>39.6±16.9</td>
<td>p&lt;0.001</td>
<td>38.1±16.6</td>
</tr>
<tr>
<td>MGLG</td>
<td>1.10±1.17</td>
<td>p=0.012</td>
<td>1.00±1.02</td>
</tr>
<tr>
<td>DED</td>
<td>n (%): 6 (30)</td>
<td>p=0.005</td>
<td>n (%): 11 (28.2)</td>
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</tbody>
</table>

ETR: Erythematotelangiectatic Rosacea; PPR: Papulopustular Rosacea; PR: Phymatous rosacea
MGD: Meibomian Gland Dysfunction; MGLR: Meibomian Gland Loss Rate; MGLG: Meibomian Gland Loss Grade; DED: Dry Eye Disease