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Original Article

The Possible Relation of *Demodex* and Facial Erythema in Connective Tissue Diseases

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Abstract

Background: We aimed to investigate the frequency of *Demodex* infestation and clinical implications in connective tissue disease patients with facial erythema.

Methods: Patients diagnosed with a connective tissue disease and had facial erythema were consecutively enrolled in the study from 2019-2020. An age and gender matched control group was formed from healthy volunteers. Presence of *Demodex* was investigated by standardized skin surface biopsy. Number of *Demodex* mites over 5 per centimeter square was considered meaningful for infestation. Topical or systemic metronidazole treatment was given to the connective tissue disease patients with *Demodex* infestation. Facial erythema visual analog scale was questioned in patients at treatment onset and one month after.

Results: A total of 31 connective tissue disease patients with facial erythema were enrolled. Control group included 31 healthy volunteers. Demographics and comorbidities were similar between groups. *Demodex* infestation was present in 58.1% of the disease group and in 25.8% of the control group (P=0.01). Pruritus was the most common symptom in patients with infestation. Median (IQR) facial erythema visual analog scale score was 6 (3) at treatment onset and was 2 (2.5) one month later (P<0.001).

Conclusion: When evaluating facial cutaneous lesions, *Demodex* infestation should not be overlooked in a patient group like connective tissue diseases with dysfunctional immune system.

Introduction

Connective tissue diseases (CTD) are rare conditions with uncertain etiology, showing mostly female predominance, characterized by autoantibody production. Along with various other organ systems, skin is frequently involved in CTDs such as dermatomyositis, systemic sclerosis, Sjögren's disease and lupus (1, 2). Recognition of cutaneous features of CTD contributes to proper diagnosis and initiation of appropriate treatment which may prevent disease related mortality and morbidity.

Facial erythema is a clinical finding that occurs because of cutaneous blood vessel dilatation and increased blood flow to the skin. Transient facial erythema due to emotional states regressed in hours and can occur in almost all healthy people. In addition, facial erythema with longer duration is also a common cutaneous manifestation in several CTDs (1, 2).

Demodex is a genus of mites resides in pilosebaceous units of mammals as an ectoparasite. Approximately 140 different species have been identified in mammals yet; only *D. brevis* and *D. folliculorum* were isolated in humans (3). *Demodex* can be detected in healthy individuals with an increasing prevalence as age advances, reaching nearly 95% in the elderly (3, 4).

Demodex ectoparasites (*D. brevis* and *D. folliculorum)* reside is in pilosebaceous units in facial skin, eyelash follicles and eyelid Meibomian glands (5). *D. folliculorum* generally placed more superficially while *D. brevis* deeper penetrates to glands. The true role of the ectoparasites in normal skin condition is yet to be clarified. They assumed to feed on human sebum and have a commensal relation with humans (6). However, when *Demodex* density exceeds a threshold, a pathological process termed demodicosis, which affects facial skin and eyelids, may initiate (7). SSSB followed by microscopic evaluation of the gathered sample is a well established, easy to apply, minimally invasive method commonly used to determine the *Demodex* density (8). Presence of at least 5 *Demodex* mites per centimeter square confirms infestation (9).

Pathogenic role of *Demodex* mites have been demonstrated in animals, likewise, *Demodex* can cause harm in immunocompromised humans as an opportunistic pathogen (6). *Demodex* infestation may lead to cause skin barrier dysfunction by causing obstruction of hair follicles and sebaceous glands. Normally *Demodex* suppress the toll-like receptor (TLR) pathway of the host, however, increased density of the parasites may lead to an inflammatory response via TLR 2 in the host causing inflammatory changes in the skin (10, 11). Several manifestations of *Demodex* infestation have been described in humans such as rosacea-like demodicosis (facial erythema), pityriasis folliculorum, perioral dermatitis and blepharitis (10, 11).

Demodex infestation may be mimicking in cutaneous manifestation in CTD such as facial erythema. In this situation, patients may be misdiagnosed as cutaneous manifestations of CTD. In this study, our aim was to investigate frequency of *Demodex* infestation and clinical implications in CTD patients with facial erythema.

Methods

Among subjects who admitted to Rheumatology Clinic of Ankara City Hospital, Ankara, Turkey between June 2019 and January 2020, patients diagnosed with a CTD and had facial erythema were consecutively enrolled in the study upon consent for participation. In all patients, the diagnosis of the CTD was confirmed by the same researcher (AE) in accordance with the respective classification/diagnostic criteria for each CTD. Demographics, comorbidities, smoking status, type of CTD and complaints regarding facial

erythema were recorded. An age and gender matched control group was formed from consecutive healthy volunteers without any systemic rheumatic disease.

Facial erythema was defined as the presence of erythematous elementary lesion in any of the face areas such as forehead, cheeks, chin and nose (Fig. 1A and 1B). All patients with facial erythema were referred to the same dermatologist and lesions were confirmed (FE). Presence of *Demodex* was also investigated by the same researcher in all subjects. Two samples for each patient were collected from erythematous lesions on the face by standardized skin surface biopsy (SSSB) by using cyanoacrylate as glue to attach a glass slide to the skin. Slides were kept in contact with the skin until the glue dries (approximately one minute), then gently removed. In control group, samples were collected with same method from both cheeks. Application of any skin product was avoided in all subjects on sampling day. Slides were examined under light microscope after applying immersion oil, right after sampling. Number of *Demodex* mites over 5 per centimeter square was considered meaningful for infestation (Fig. 1C).

Topical or systemic metronidazole treatment was given to the CTD patients with *Demodex* infestation. Facial erythema visual analog scale (VAS) was questioned in patients at treatment onset and one month after. Sun protection and dietary regulation was also suggested to patients during one-month follow-up.

The study protocol was approved by the Ankara City Hospital Ethics Committee (date: 09/06/2021, approval number: E1-21-1860). A written informed consent was obtained from each participant. The study was conducted in accordance with the principles of the Helsinki Declaration.

Statistical analyses were made by using Statistical Package for the Social Sciences (SPSS) 22.0 software (IBM Corp., Armonk, NY, USA). Shapiro-Wilk's test was used to determine the distribution of the data. The distribution of continuous data was expressed either as mean ± standard deviation (SD) or as median and interquartile range (IQR) according to normality. Continuous variables were compared by using either student t-test or Mann-Whitney-U test according to normality. For comparison of categorical variables x^2 test was used and the outcomes were expressed as number and percentages. P values below 0.05 were considered statistically significant.

Results

Thirty-one CTD patients with facial erythema were enrolled in the study. CTD types comprise undifferentiated CTD in 14 (45.2%) patients (meeting the classification criteria (12)), SLE in 10 (32.3%) patients (meeting 2019 *American College of Rheumatology* (ACR) / *European League Against Rheumatism* (EULAR) classification criteria (13)), Sjögren's disease in 6 (19.4%) patients (meeting 2016 ACR/EULAR classification criteria (14)) and SLE with secondary antiphospholipid antibody syndrome (APS) in 1 (3.2%) patient (meeting 2019 SLE ACR/EULAR classification criteria (9) and Sapporo APS criteria (15)). Control group included 31 healthy volunteers. The mean (SD) age in the patient group was 40.90 (12.04) years, while the mean (SD) age in control group was 43.67 (8.4) (P = 0.29, Table 1). All of our participants were women. Frequency of active smokers was 33.3% in patient group and 15.4% in control group (P=0.26). Distribution of comorbidities was also similar. *Demodex* infestation was present in 58.1% of the CTD group and in 25.8% of the control group (P = 0.01, Table 1).

Comorbidities and frequency of symptoms in CTD patients with and without *Demodex* infestation are presented in Table 2. Pruritus was the most common symptom in CTD patients with infestation (44.4 %).

After treatment, symptoms regressed in 14 (77.7%) of the CTD patients with *Demodex* infestation. Median (IQR) facial erythema VAS was 6 (three) at treatment onset and was 2 (2.5) one month after (P <0.001).

Table 1: Demographics and frequency of *Demodex* infestation in CTD patients with facial erythema and healthy controls

Variable	CTD group (n=31)	Control group (n:31)	P
Age, years, mean (SD)	40.9 (12.04)	43.67 (8.4)	0.29
Gender, female, n(%)	31 (100)	31 (100)	1
Demodex positive, n(%)	18 (58.1)	8 (25.8)	0.01

CTD: connective tissue disease, SD: standard deviation, n: number

Table 2: Symptoms, smoking status and comorbidities in CTD patients with and without *Demodex* infestation

Variable	*Demodex* positive CTD (n=18)	*Demodex* negative CTD (n=13)	p
Presence of pruritus, n (%)	8 (44.4)	2 (15.4)	0.088
Presence of burning sensation, n (%)	5 (27.8)	3 (23.1)	0.76
Active smoker, n (%)	6 (33.3)	2 (15.4)	0.26
Presence of any comorbidity, n (%)	8 (44.4)	5 (38.5)	0.73
CVD, n (%)	1 (5.6)	2 (5.4)	0.36
HT, n (%)	5 (27.8)	2 (15.4)	0.41
DM, n (%)	1 (5.6)	2 (5.4)	0.36
Thyroid disease, n (%)	1 (5.6)	1 (7.7)	0.81

CTD: connective tissue disease, SD: standard deviation, n: number, CVD: cerebrovascular disease, HT: hypertension, DM: diabetes mellitus

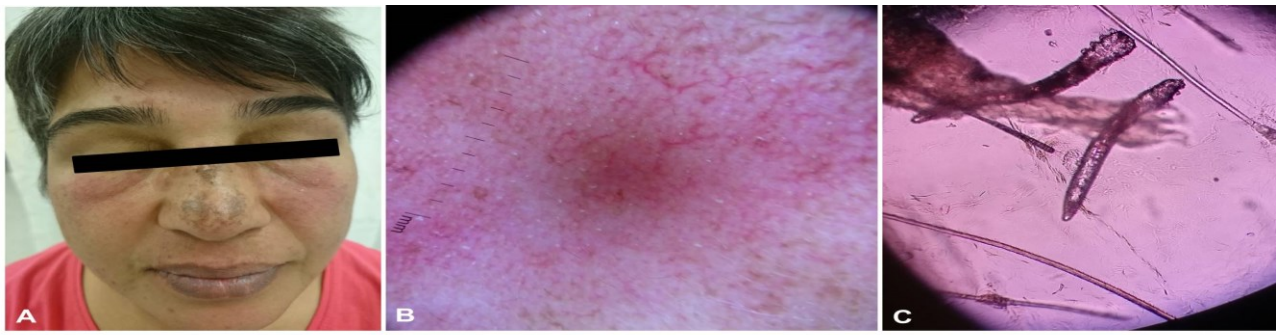

Fig. 1: A: Facial erythematous lesions in a systemic lupus erythematosus patient with *Demodex* infestation, B: Dermatoscopic view of the erythematous lesions. C: *Demodex* mites under light microscope sampled from the same patient

Discussion

Our results demonstrated an increased frequency of *Demodex* infestation in CTD patients with facial erythema. Pruritus was more frequent in CTD patients with facial erythema when *Demodex* infestation was present without reaching statistical significance. Facial erythema VAS significantly improved with antiparasitic treatment in patients with *Demodex* infestation.

Various rheumatic diseases have cutaneous manifestations altering quality of life (16). Furthermore, cutaneous lesions have diagnostic importance in rheumatic diseases and included in classification criteria for most conditions.

Likewise, presence of cutaneous manifestations is also evaluated while measuring disease activity. Therefore, decent assessment of any skin symptom with accurate differential diagnosis has great importance in rheumatic conditions, since false interpretation can lead to misdiagnosis and improper treatment.

Facial erythema can be observed in a variety of conditions including rosacea, photodamage, SLE, seborrheic dermatitis, psoriasis and keratosis pilaris rubra (17). Although *Demodex* infestations have not certainly been associated with facial erythema, a relation between *Demodex* density and severity of facial erythema have been reported (7). Furthermore, *Demodex* mites have been linked to chronic inflammation in a variety of areas and the increased frequency of demodicosis has been associated with immune system dysfunctions (6, 9, 10). *Demodex* infestation has been high in hematological malignancies treated with chemotherapy (18). CTDs are chronic autoimmune conditions also characterized by a dysfunctional immune system. In our study, *Demodex* infestation was significantly more frequent in CTD patients with facial erythema in comparison to healthy controls (58.1% vs 25.8%). Similar to our results, increased *Demodex* infestation has also been reported in rheumatoid arthritis patients when compared to healthy controls (44% vs 15.7%, $P<0.001$) (19). Likewise, 50% more *Demodex* infestation was observed in discoid lupus erythematosus patients (20). On the other hand, there was no statistically significant difference in *Demodex* mite presence between control group (No. of infested persons/No. of examined persons; 23/75, 30.6%) and RA patients group (24/72, 33.3%) (21). Similar to this result, no statistically significant differences were found in the rate of *Demodex* mites between patients with RA (5/41, 12.1%) and control group (2/27, 7.4%) (22).

Facial demodicosis have been associated with overt symptoms like pruritus, erythema, papulopustular and granulomatous rosacea as well as more vague effects like pityriasis follicularum and folliculitis (23, 24). In our study, pruritus was present in 44.4% of patients with *Demodex* infestation while only 15.4 % patients without *Demodex* had pruritus. *D. brevis* mostly causes a symmetrical, malar, papulopustular eruption while *D. follicularum* is mostly related with erythema on forehead and nose (25). We did not investigate *Demodex* subspecies in our study.

Demodex is treated with antiparasitic agents such as metronidazole, permethrine, benzyl benzoate, crotamiton, lindane and sulphur. On the other hand, CTD related cutaneous lesions are treated with topical or systemic immunosuppressive or immunomodulatory agents such as steroids and hydroxychloroquine. Since therapeutic approach in these two conditions differs majorly, a misdiagnosis has to be avoided. In our study, with appropriate antiparasitic treatment, facial erythema and other symptoms significantly regressed in patients with *Demodex* infestation.

Small sample size was a major limitation for our study. Furthermore, *Demodex* density might be affected by sampling location for SSSB, since it has been reported that *Demodex* density varies between facial areas like nose, forehead or cheeks (26). Nevertheless, to our best knowledge, this is the first study to evaluate *Demodex* infestation in CTDs.

Conclusion

Although facial erythema is a common manifestation in CTDs, primary condition may not always be the underlying culprit. As an opportunistic pathogen, *Demodex* infestation should not be overlooked in a patient group like CTD with dysfunctional immune system. Misdiagnosis may lead to further altered quality of life and inappropriate treatment. Larger studies would further elucidate the frequency of *Demodex* infestation and clinical implications in CTDs.

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Conflicts of interest

The authors declare no conflicts of interest.

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