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Do Hematologic Cancers Increase the Frequency of *Demodex* Spp.?

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Abstract

Background and aim: Demodicosis is a parasitic skin disease caused by *D. folliculorum* and *D. brevis*, and is also known as hair follicle mite. The aim of this study was to determine the prevalence of *D. folliculorum* and *D. brevis* in hematologic cancer patients and to investigate their relation with chemotherapy.

Materials and methods: Sixty-six hematologic cancer patients and 60 healthy individuals with similar age and sex were included in the study. Of the patients with hematological cancer, 50 received chemotherapy and 16 did not receive chemotherapy. The demographic characteristics of the patients were noted. Samples were taken from the cheeks, nose, chin and forehead of the participants with standardized skin surface biopsy and examined in light microscopy at 40x and 100x magnifications to determine the mite density in cm^2. Demodicosis was assessed as positive if 5 or more *Demodex spp.* were seen per cm^2.

Results: *Demodex spp.* was positive in 19 (28.78%) of the cancer patients and 3 (5%) of the control group. The prevalence of *Demodex spp.* was significantly higher in the patient group ($p<0.001$). The mean mite count (31.31/cm^2), in the patient group was also significantly higher than the control group (1.08/cm^2), ($p<0.001$). *Demodex spp.* density was 38.94/cm^2 in patients receiving chemotherapy and 7.50/cm^2 in patients not receiving chemotherapy, and the difference between them was statistically significant ($p<0.001$).

Conclusion: In conclusion, our study showed that patients with hematological cancer were infected with *Demodex spp.* more than controls and that the density of *Demodex spp.* was significantly increased in chemotherapy group. It should be kept in mind that *Demodex spp.* increases with weakening of the immune system and may cause skin lesions in hematologic cancer patients, especially in chemotherapy receiving patients.

Keywords: *Demodex*; Hematology; Cancer

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Introduction

Demodex spp. is a mite from the Demodicidea family of the Prostigmata order of Arachnida class; and it is the mandatory commensals of the pilosebaceous units. Despite there are lots of *Demodex* species, only two species can live as parasites in the human body [1]. *D. folliculorum*, which has long opistosome, lives in pilosebaceous units as single or groups whereas *D. brevis*, which has short opistosome, lives mostly in sebaceous and meibomian glands as single [2,3]. It has been found that *D. folliculorum* is always located posterioinferior of the hair follicle and feeds with the contents of the follicular epithelial cells by puncturing the cell wall with knife-like chelicera. *D. brevis* feeds with the epithelia of the sebaceous glands in the same way [2,3]. In humans, forehead, cheeks, nose, chin and nasolabial region are the most common sites of infestation and it can rarely be located in different parts of the body such as neck, scalp, ear, chest, back, breast, hip and genital organs [3]. As the age increases, the incidence of *Demodex spp.* infestation also increases; the prevalence is 100% in middle-aged and elderly adults [4-6]. The density of *Demodex spp.* is lower than 5 *Demodex spp.*/cm^2 in the general population [4,7]. *Demodex spp.* is passed to infants through close contact or breastfeeding immediately after birth, but due to low sebum production, *Demodex spp.* density is low in children [4,5,8]. How

the *Demodex spp.* becomes pathogenic is still controversial, but it is thought that increased number of *Demodex spp.* or transition to the dermis could cause this infestation [7].

Demodex spp. could play a role in the etiopathogenesis of diseases such as acne rosacea, acne vulgaris, blepharitis, perioral dermatitis, pustular folliculitis, papillary pustular lesions of the scalp, pityriasis folliculorum, chronic renal failure, and basal cell carcinoma, pustular lesions in acquired immunodeficiency syndrome, keratoconjunctivitis, recurrent chalazions and meibomian gland dysfunctions [9-18]. For the diagnosis of the disease, cellophane tape method, preparation of skin scrapings in potassium hydroxide, punch biopsy and standardized skin surface biopsy can be used [2,4,7].

Malignant hematologic diseases are generally divided into lymphoid and myeloid neoplasms. The myeloid malignancies are myelodysplastic syndromes, myeloproliferative neoplasms (chronic myeloid leukemia, primary myelofibrosis, polycythaemia vera, essential thrombocytosis), acute myeloid leukemia, myeloid sarcoma and myeloid neoplasms with eosinophilia. The most important lymphoid malignancies are chronic lymphocytic leukemia/small lymphocytic lymphoma, hairy cell leukemia, plasma cell myeloma, solitary plasmacytoma, non-Hodgkin's lymphoma, Hodgkin's lymphoma, lymphoplasmacytic lymphoma and acute lymphoblastic leukemia [10,11]. Bone marrow infiltration, dysfunctions of T and B cells and hypogammaglobulinemia are the main causes of immunosuppression in hematologic malignities. In addition, neutropenia and lymphopenia, which leads to mucosal injury, are the side effects of various chemotherapeutic agents [12]. There are studies reporting that the incidence of *Demodex spp.* may increase due to immunosuppression for such reasons as immunosuppressive drug usage, advanced age, etc. However, the patogenity of this increased *Demodex spp.* is controversial [9-18].

We have an original study published in 2007 regarding the occurrence of *Demodex spp.* in patients with rheumatoid arthritis [13]. To the best of our knowledge, our current study is the first study investigating the presence and density of *D. folliculorum* and *D. brevis* in hematologic cancer patients. Besides, it is also the first study investigating *D. folliculorum* and *D. brevis* in chemotherapy patients.

The present study aimed to investigate the prevalence and infestation of *D. folliculorum* and *D. brevis* in patients with haematological cancers and to define if chemotherapy influences the presence of *Demodex* mites or not.

Materials and Methods

Patients and groups

Sixty-six hematologic cancer patients (40 males and 26 females) aged between 19-83 years who applied to haematology clinic in Hatay Mustafa Kemal University Medical Faculty between February 2016 and July 2016 and 60 healthy controls (38 males and 22 females) aged between 19-82 years were included in the study. Of the patients with haematological cancer, 50 received chemotherapy and 16 did not receive chemotherapy. Demographic (sex and age) and clinical properties (the type of the cancer, chemotherapy ±, and the density of *Demodex* mite) were obtained from patients records. Other properties about chemotherapy administration and type of the dermatological findings were obtained from dermatology clinic archives. Patients who were under the age of 18 years and who had disabilities, pregnancy, diabetes mellitus, autoimmune disease, allergic disease, alcoholism or/and those without authority to sign were not included in the study.

Ethics committee approval and informed consent

Ethics committee approval was obtained adhering to the Declaration of Helsinki. Informed consent was obtained from all participants. Demographic characteristics of the patients were recorded and all the subjects were informed about the parasite and sampling method before the study. Participation in the study was voluntary.

Collection and examination of the samples

For the diagnosis of the disease standardized skin surface biopsy was used. To detect *Demodex* mites non-invasively, after dropping a drop of cyanoacrylate on the slide, a sample was obtained by adhering this slide to the skin area to be investigated. Thus, a part of the skin containing the pilosebaceous unit was transferred to the slide. 2-3 drops of glycerine were added to the slides and then covered with coverslip. This ensures that the mites remain alive and mobile so that they can be examined more easily. Samples were examined by light microscopy at 40x and 100x magnification [7]. Demodicosis was assessed as positive if 5 or more *Demodex spp.* were seen per cm^2. The diagnosis of all *Demodex* species visible in the light microscope was made by the parasitologist on the basis of the diagnostic criteria specified in the relevant literature [19]. On microscopic examination, if *Demodex* was found embedded in the hair follicle, it was allowed to come out of the follicle by gently pressing on the slide. *Demodex* was diagnosed after the entire body was seen. For diagnosis, the length of *Demodex* body, the ratio of opistosome to idiosoma, the pointed or rounded formation of the terminal portion of the opistosome, development stages, leg and mouth pieces were examined. The sample material was considered positive for *Demodex* when the larvae, nymph or adult of *D. folliculorum* or *D. brevis* were found in the slides. The samples were collected at any time of day regardless of whether the medication was taken or not.

Statistical analysis

In the statistical analysis of this study, descriptive data were given as mean ± Standard Deviation (SD) in the SPSS 22.0 program (SPSS Inc., Chicago, IL, USA). Shapiro-Wilk or test was used for testing normality. Student's t-test was used to determine differences between patient and controls groups and between subgroups. Alpha significance level less than 0.05 were considered statistically significant.

Results

The ages of the patient group were between 19 and 83 years, with a mean age of 62.4 ± 14.8. Forty patients (60.6%) were

male, 26 (39.4%) were female. The ages of the control group were between 19 and 82 years, with a mean age of 61.7 ± 15.0. Thirty-seven (61.7%) were male, 23 (38.3%) were female. There was no statistically significant difference between the patient and the control group in terms of age and gender (p=0.9 and p=0.9 respectively). According to the present study, 19 of the 66 (28.8%) patients with hematologic cancer were positive for the *Demodex* species, but only 3 cases of the control group were positive. This difference was statistically significant **(Table 1).**

Demodex spp. was detected in 28.8% of the patient group (mean 31.31/cm^2); 1813 of them were *D. folliculorum* (mean 27.14/cm^2) and 254 of them were *D. brevis* (mean 3.84/cm^2). In the control group *Demodex spp.* was detected as 5%; all of them were *D. folliculorum* (mean 1.08/cm^2). *D. brevis* was not found in the control group. When the patient and control group were compared, it was found that the difference was statistically significant (p=0.001).

Demodex spp. was detected in 34%of the chemotherapy receiving patients (mean 38.94/cm^2); 1681 of them were *D. folliculorum* (mean 33.62/cm^2) and 244 of them were *D. brevis* (mean 4.88/cm^2). *Demodex spp.* was detected in 12.5% of the cancer patients without chemotherapy; 171 of them were *D. folliculorum* (mean 6.88/cm^2) and 10 of them were *D. brevis* (mean 0.62/cm^2). When the groups receiving and not receiving chemotherapy were compared, it was seen that the difference was statistically significant (p<0.001).

When the distribution of *Demodex spp.* in the face region was examined in the patients, it was determined that the maximum of the infestation was in the cheek area (total 1203, mean 18.22/cm^2). This was followed by the nose area (total 339, mean 5.13/cm^2), forehead area (total 156, mean 2.36/cm^2) and jaw area (total 75, mean 1.13/cm^2) **(Table 2).** When the distribution of *Demodex spp.* in the face region was examined in the control group, the infestation was detected only in the cheek area (total 25, mean 0.41/cm^2). When the face regions were compared in terms of *Demodex spp.* the differences were statistically significant (p<0.001).

Diagnosis of the patients were 20 (30.3%) Multiple Myeloma (MM), 11 (16.7%) Non-Hodgkin Lymphoma (NHL), 10 (15.2%) Chronic Lymphocytic Leukemia (CLL), 8 (12.1%) Chronic Myeloid Leukemia (CML), 4 (6.1%) Essential Thrombocytosis (ET), 2 (3%) Acute Lymphoblastic Leukemia (ALL), 2 (3%) Acute Myeloblastic Leukemia (AML), 2 (3%) Hodgkin Lymphoma (HL), 2 (3%) Myelodysplastic Syndrome (MDS), 2 (3%) Polycythemia Vera (PV), 1 (1.5%) Hairy Cell Leukemia (HCL), 1 (1.5%) Primary Myelofibrosis (PMF) and 1 (1.5%) Waldenstrom Macroglobulinemia (WM). Nineteen (28.8%) patients had positive *D. folliculorum*, 47 (71.2%) were negative. There were no significant differences in terms of cancer type, gender and age **(Table 3).**

Discussion

Demodex spp. species that cause infestation in humans are *D. folliculorum* and *D. brevis*, and the only hosts are humans. The main food source of the *Demodex* mites, which live as parasites in human skin, are follicular epithelial cells and sebum [19]. Studies have shown that these mites destroy follicular and sebaceous epithelial cells with sharp mouthpieces and claws, destroy the skin barrier and form lymphocytic infiltrates around the follicle. After the penetration to the dermis, the mite causes an immune response to chitin, and mite densities increase when the immune system is suppressed or inadequate (congenital or aquired) [20-22]. HLA (human leukocyte antigen) haplotypes, T and B lymphocytes and NK (natural killer) cells play an important role in the immune response. In studies investigating the relationship between demodicosis and HLA, it has been emphasized that HLA A2 haplotype is protective against demodicosis, and individuals with this phenotype are 3 times more resistant to demodicosis. It has been informed that the individuals who have HLA CW2 and HLA CW4 haplotypes develop demodicosis five times more and

Table 1 Distribution of *Demodex* spp. according to the patients and the control group.

Variables	*Demodex* spp.		Total	P-value
	Negative (N/%)	Positive (N/%)		
Patients	47 (71.2)	19 (28.8)	66	0.0001
Control	57(95)	3 (5)	60	

Table 2 Distribution of *Demodex* spp. in the face region in patients.

Variables		Prevalence of *Demodex* spp. (%)			Number of *Demodex* spp. /cm^2		
		N	%	P	Mean	Total	P
D. folliculorum	Right cheek	19	28.8	0.001	9.13	573	0.001
	Left cheek	19	28.8	0.001	9.09	575	0.001
	Forehead	6	9.1	0.186	2.36	156	0.092
	Nose	17	25.8	0.001	5.13	319	0.001
	Chin	4	6.1	0.053	1.13	75	0.070
D. brevis	Right cheek	9	13.6	0.013	1.46	97	0.005
	Left cheek	-	-	-	1.31	87	0.005
	Forehead	2	3	0.174	0.45	30	0.177
	Nose	4	6.1	0.053	0.45	30	0.067
	Chin	-	-	-	-	-	

Table 3 Distribution of *Demodex* spp. according to patients diagnosis, gender and age groups.

Factors	Variables	Negative (N/%)	Positive (N/%)	Total	P-value
Diagnosis	ALL	2 (100)	0 (0)	2	0.321
	AML	1 (50)	1 (50)	2	
	ET	4 (100)	0 (0)	4	
	HCL	0 (0)	1 (100)	1	
	HL	2 (100)	0 (0)	2	
	CLL	7 (70)	3 (30)	10	
	CML	6 (75)	2 (25)	8	
	MDS	1 (50)	1 (50)	2	0.507
	MM	13 (65)	7 (35)	20	
	NHL	8 (72.7)	3 (27.3)	11	
	PMF	1 (100)	0 (0)	1	
	PV	2 (100)	0 (0)	2	
	WM	0 (0)	1 (100)	1	
Gender	Females	19 (73)	7 (27)	26	
	Males	28 (70)	12 (30)	40	
Age groups	18-35	1 (50)	1 (50)	2	0.250
	36-55	13 (86.6)	2 (13.4)	15	
	>55	33 (67.3)	16 (32.7)	49	
Total		47 (71.2)	19 (28.8)	66	

that *Demodex* intensity increases in these individuals depending on increased lymphocytes and NK apoptosis (programmed cell death) [3,22,23].

In various studies, *Demodex* infestations have been reported in patients with actinic keratosis, non-melanoma skin cancers, basal cell carcinoma, hematologic and urologic malignancies. Moreover, the incidence of the mites is increased in patients with acquired immunodeficiency syndrome, diabetes mellitus and children with malnutrition. These studies suggested that immunosuppression plays an important role in Demodicosis [3,13-17]. The results of the studies on the incidence of *Demodex spp.* in patients receiving topical or systemically steroids are controversial. Bonnar et al. [5] reported that incidence of *Demodex spp.* was significantly higherin patients receiving topical steroids. Although many studies claim that the immune system limits the number of mites, there is no agreement on this issue. Forton et al. [4] investigated the intensity of *Demodex spp.* in 21 patients with HIV and found no increase. Our patient population was generally old and most of them had received chemotherapy during the study. Immunosuppression levels of these patients were high and the incidence of *Demodex spp.* was found higher in patients with hematologic malignancies when compared to control group in our study.

Demodex spp. was investigated in patients with renal failure, rheumatoid arthritis and phototherapy treatment and following results were found respectively: 40.2% (mean 6.12/cm^2) in the patient group and 29.8% (mean 0.31/cm^2) in the control group; 12% in the patient group and 8% in the control group; 28.9% (mean 3.22 /cm^2) in patient group and 7% (mean 0.97/cm^2) in control group [9,13]. In our study, *Demodex spp.* was detected ions 28.8% in 66 patients with haematological cancer (mean 31.31/cm^2) and 5% in 60 healthy controls (mean 1.08/cm^2), consistent with the above mentioned studies. This increase in *Demodex spp.* proliferation in hematologic cancer patients was thought to be a consequence of impaired immune response.

Demodex spp. was detected in 28.8% of the patient group (mean 31.31/cm^2); 1813 of them were *D. folliculorum* (mean 27.14/cm^2) and 254 of them were *D. brevis* (mean 3.84/cm^2). In the control group *Demodex spp.* was detected as%5; all of them were *D. folliculorum* (mean 1.08/cm^2). *D. brevis* was not found in the control group. When the patient and control group were compared, it was found that the difference was statistically significant (p<0.001).

In our study, *D. folliculorum* infestation was found to be more frequent and more intense than *D. brevis* in consistent with the literature [18,24]. This may be due to the fact that *D. brevis* lives deeper than skin surface (sebaceous glands below hair follicles) and *D. folliculorum* lives on the upward facing side of hair follicles (closer to skin surface) and is therefore easier to isolate.

Various studies have reported that *Demodex spp.* can be placed in various parts of the body such as the forehead, cheek, chin, nose and nasolabial regions in the face, genital regions, breast, scalp, neck and external auditory canal but it has been reported that most of the infestations are in the cheek area [9,17,18,25]. In our study, it was also determined that the maximum of the infestation was in the cheek area (total 1203, mean 18.22/cm^2). This was followed by the nose area (total 339, mean 5.13/cm^2), forehead area (total 156, mean 2.36/cm^2) and jaw area (total 75, mean 1.13/cm^2).

In a study comparing 50 patients with haematological malignancy (leukemia and lymphoma) with 50 healthy controls, *D. folliculorum* infestation rates were found higher in the patient group. The highest incidences of *Demodex spp.* were found in patients with AML, NHL, ALL, CLL and CML [15]. In another study where 101 solid cancer patients were included, the incidence of *Demodex*

spp. was found to be the highest in patients with breast cancer [17]. In our study, there was no statistically significant difference in terms of cancer type. This may be due to the small size of our patient population or the fact that our patients have not had solid cancer.

Chemotherapy is a treatment that is used to kill cancer cells, and there are many chemotherapy drugs that affect various cancer types. The common feature of all chemotherapy drugs is that they weaken the immune system. Therefore, both the cancer itself and the chemotherapeutic agents disrupt the immune system. This situation makes the patients more vulnerable to various opportunistic infectious agents.

Kulaç et al. [20] investigated *Demodex spp.* in 45 patients who received phototherapy for various reasons and 43 healthy subjects. *Demodex spp.* was detected in 13 (28.9%) of the 45 patients and in 3 (7%) of 43 healthy subjects in this study. The authors reported that this difference was statistically significant and the suppression of the immune system resulted in increased *Demodex spp.* In our study, *Demodex spp.* was found statistically significantly higher in patients who received chemotherapy than patients who did not receive chemotherapy. Based on these findings, it can be concluded that both the disease and the immunosuppressive effect of chemotherapy make the patients vulnerable to *Demodex spp.* infestation.

Demodex mites are not found in new-borns, but the numbers are ever increasing in infantile, childhood, puberty and adulthood [21]. Seyhan et al. [15] reported *Demodex spp.* in 14 of 50 hematologic cancer patients who between 17-77 years (mean 47.4 ± 18.2); Karıncaoğlu et al. [9] reported *Demodex spp.* in 27 of 67 chronic renal failure patients who between 16-80 years (mean 51.0 ± 17.1); Çiftçi et al. [13] reported *Demodex spp.* in 5 of 41 rheumatoid arthritis patients between 23-75 years (mean 54.4 ± 13.6) years. In our study, *Demodex spp.* positivity was detected in 19 of 66 hematologic cancer patients aged 19-83 years (mean 62.4 ± 14.8). Most of our patients were advanced aged and this might explain why we couldn't find any difference.

When *Demodex spp.* was investigated in terms of gender, in a study conducted by Sönmez et al. [17], 25.5% of men and 37.0% of women found *Demodex spp.* positive. In our study, *Demodex spp.* was examined in terms of gender, there was no significant difference, which was in consistent with the literature [18-25].

Conclusion

In conclusion, our findings suggest that immunosuppressive conditions such as cancer and chemotherapy treatment may lead to *Demodex spp.* infestation. For this reason, clinicians should be more cautious when evaluating immunosuppressed patients, and if there is a secondary infection suspicion, these patients should immediately be consulted to the relevant departments.

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