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Associations between *Demodex* species infestation and various types of cancer

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Abstract

Tumor-associated immune system cells secrete protease and cytokines that can inhibit the immune response. In particular, T-cell effector functions could be inhibited, potentially causing an increase in parasitic infestations. *Demodex* species are common inhabitants of normal hair follicles. Humans are the specific host for two species *Demodex folliculorum* and *D. brevis.* The aim of this study was to investigate the incidence and infestation of *D. folliculorum* and *D. brevis* in patients with cancer. In the present study, 101 patients with cancer were selected from among patients who were diagnosed and treated for cancer. The cancer patients were divided into four groups according to cancer type. Slides were examined for parasites using light microscopy at magnifications of ×40 and ×100. Infestation was defined as having at least five living parasites/cm^2 of skin. The ages of the patients with cancer ranged between 38 and 82 years, with a mean of 65.5±10.1 years. It was determined that 77 of the 101 (76.2%) cancer patients were positive for *Demodex* species. Infestation was positive in 18 (47.4%) of the 38 cases in the breast cancer group, 7 (29.2%) of the 24 cases in the lung cancer group, 5 (18.5%) of the 27 cases in the gastrointestinal system cancer group, and 2 (16.7%) of the 12 cases in the urogenital system cancer group. Results showed that the rate of *Demodex* species infestation was higher in patients with breast cancer. Thus, cancer – and particularly breast cancer – is a risk factor for *Demodex* species infestation.

Keywords

Cancer, risk factor, *Demodex*, infestation

Introduction

Cancer is a leading cause of death worldwide. Additionally, deaths from cancer worldwide are projected to continue to rise, with an estimated 13.1 million in 2030 (Ferlay *et. al.* 2008). Lung, stomach, liver, colon, and breast cancer are the most frequent causes of cancer deaths, but this differ between the genders. Anticancer drugs are commonly used to treat the disease, most of which have immunosuppressive effects. Additionally, cancer immunosuppression, which favors tumor progression and metastasis, is mediated by constitution of an immunosuppressive network comprising mediators such as interleukin-10 (IL-10) and transforming growth factor-β (TGF-β) (Yang and Carbone 2004). These create a micro-environment that counters immune activation and attack. Modulation of the human immune response by cancer could lead to parasite establishment rates that increase along with the parasite burden but which are not dependent on hyperendemic annual transmission potentials. Presently, increasing evidence suggests that immune mechanisms are involved in the pathogenesis of many parasitic infections. Paradoxically, hyporesponsiveness to antigen-specific and polyclonal stimuli in chronic parasitic infections could be related to secretion of immunosuppressive cytokines (i.e., IL-10 and TGF-β) by antigen-presenting cells and regulatory T cells.

The most common permanent ectoparasites include *Demodex folliculorum*, which exists either alone or in groups in the spaces of hair follicles, particularly on the face, and *D. brevis*, which lives deeper in the sebaceous and meibomian glands (Jansen *et al*. 2001, Baima and Sticherling 2002, Dong and Duncan 2006). Humans are the specific host for two species: *D. folliculorum* and *D. brevis*. *D. folliculorum* is more common than *D. brevis*. *Demodex* species can be found anywhere on the skin but exist most frequently in areas in which the number of sebaceous glands is highest, such as the nose, nasolabial folds, eyelids, cheek, forehead, chin, and neck (Ak-

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deniz *et al.* 2002). Most people are infested with these mites, but clinical symptoms of skin demodicidosis develop only rarely (Akilov and Mumcuoglu 2003). However, in humans, there is mounting evidence that *Demodex* species, like other cutaneous microflora, may be opportunistic pathogens–that is, they have the potential to change their status from commensals to parasites if the host cutaneous environment facilitates their proliferation (Dahl *et al.* 2004; Whitfeld *et al.* 2011). Several factors could allow proliferation of *Demodex* species to this critical level. The role of suppression of the host immune response in the facilitation of *Demodex* proliferation is suggested (Gerber *et al.* 2011), and it has been reported that a hyporesponsiveness status may be associated with an increase in the density of *D. folliculorum* and demodicidosis in children with leukemia who are receiving chemotherapy (Patrizi *et al.* 1997, Damian and Rogers 2003).

The aim of the present study was to investigate the incidence and infestation of *D. folliculorum* and *D. brevis* in patients with cancer.

Materials and Methods

In the current study, 101 patients with cancer were selected from among patients diagnosed and treated for cancer between November 1, 2011 and August 1, 2012. Patient demographics (gender, age, and body mass index) and clinical characteristics (cancer type, chemotherapy status, skin type, and *Demodex* intensity) were obtained from clinic records. The patients were divided into four groups according to cancer type: breast cancer group (BCG), gastrointestinal system cancer group (GCG), lung cancer group (LCG), and urogenital system cancer group (UCG). Other classifications used for chemotherapy status and patients' dermatological findings (erythema, telangiectasia, follicular tiny papule, follicular tiny pustule, follicular scaling papule, pustule, nodule, and abscess) were obtained from dermatology clinic archives.

Exclusion criteria for patients were as follows: previously diagnosed rosacea, perioral dermatitis or any dermatosis related to *Demodex* species, immunosuppression, diabetes mellitus, autoimmune disease, allergic disease, alcoholism or/and other substance abuse, and the use of topical and systemic antibiotics within the last 4 weeks. Seventy-four patients were excluded due to unsuitable or incomplete data.

Four standardized skin surface biopsies (SSSBs) were taken from the cheek, forehead, nose, and chin. The SSSB is a noninvasive sampling method in which the superficial part of the skin and the complete follicle contents, including mites, are collected. A drop of cyanoacrylic adhesive was placed on a microscope slide, and the adhesive-bearing surface of the slide was applied to the skin. The slide was then removed from the skin surface after 2 min, one to two drops of immersion oil was placed on the sample, and the sample was covered with a cover slip. Slides were examined (a surface area of ~1 cm^2) for parasites using light microscopy at magnifications of ×40 and ×100 (Ciftci *et al.* 2007). Infestation was defined as at least living parasites/cm^2 of skin. The clinical examination, SSSB, and microscopy were performed by the same investigator.

The Pearson Chi-square (χ^2) test was used to compare the prevalence of mites and infestation rates in the patient groups. Fisher's exact test was applied when appropriate. Local statistical significance was deemed to be a p value less than 0.05 for all parameters. Analyses were performed using the SPSS 17.0 software.

Results

The ages of the patients with cancer ranged between 38 and 82 years, with a mean of 65.5±10.1 years. According to the pres-

Table I. Distribution of the *Demodex* species according to patiens group, chemotherapy, gender, and age group

Factor		Negative (0–<5) n (%)	Positive (≥5)* n (%)	Total n (%)	*p* value
Cancer groups	BCG	20 (52.6)	18 (47.4)	38 (37.6)	0.049
	LCG	17 (71.8)	7 (29.2)	24 (23.8)	
	GCG	22 (81.5)	5 (18.5)	27 (26.7)	
	UCG	10 (83.3)	2 (16.7)	12 (11.9)	
Chemotherapy	Use	34 (69.4)	15 (30.6)	49 (48.5)	0.834
	Non	35 (67.3)	17 (32.7)	52 (51.5)	
Gender	Male	35 (74.5)	12 (25.5)	47 (46.5)	0.153
	Female	34 (63.0)	20 (37.0)	54 (53.5)	
Age groups	35–45	4 (80.0)	1 (20.0)	5 (4.9)	0.598
	45–55	19 (69.4)	8 (29.6)	27 (26.7)	
	>55	46 (66.7)	23 (33.3)	69 (68.3)	
Total		**69 (68.3)**	**32 (31.7)**	**101 (100)**	

*Infestation was defined as having at least five living parasites/cm^2. Abbreviations: BCG, breast cancer group; GCG, gastrointestinal system cancer group; LCG, lung cancer group; UCG, urogenital system cancer group.

ent study, 77 of the 101 (76.2%) cancer patients were positive for the *Demodex* species. Infestation was positive in 18 (47.4%) of the 38 cases in the BCG, 7 (29.2%) of the 24 cases in the LCG, 5 (18.5%) of the 27 cases in the GCG, 2 (16.7%) of the 12 cases in the UCG. Significant differences were found in infestation levels among cancer types ($p = 0.049$), and a relationship between *Demodex* species infestation and the high infestation rate of the BCG was noted. According to the drug histories, various agents (such as cyclophosphamide, platinum agents, pyrimidine analogs, gemcitabine, anthracyclines, taxanes, etoposide, and irinotecan) were used for chemotherapy. However, the infestation rates between the given chemotherapy and no (initial) chemotherapy were not significantly different ($p = 0.834$). There was no significant difference in the infestation of *Demodex* species according to gender ($p = 0.153$). Furthermore, no significant differences were found in *Demodex* infestation according to age ($p = 0.598$). The distribution of the findings regarding *Demodex* species is shown in Table I.

Demodex species presence varied according to localization. In the present study, the highest presence was found in the cheeks and forehead in the BCG. There was a significant difference between the presence of *Demodex* species according to patient group regarding the forehead ($p = 0.006$). Other localization results showed no significant differences. The distribution of *Demodex* species according to location is shown in Table II.

Infestation rates were not significantly different according to skin type ($p=0.587$). Furthermore, neither lesion presence ($p=0.322$) nor erythema positivity ($p=0.392$) showed significant differences in infestation. Data concerning infestation in terms of dermatological parameters are shown in Table III.

In the present study, there was a significant association between BMI and cancer type; and the BCG was found to be associated with an overweight BMI. Additionally, 27 cases in the overweight BMI group, 3 in the intermediate BMI group, and 2 in the underweight BMI group were found to be infested

Table II. *Demodex* species infestation according to location

Factor		Negative n (%)	Positive n (%)	Total n (%)	*p* value
Right cheek	BCG	15 (39.5)	23 (60.5)	38 (37.6)	0.673
	LCG	10 (41.7)	14 (58.3)	24 (23.8)	
	GCG	13 (48.1)	14 (51.9)	27 (26.7)	
	UCG	7 (58.3)	5 (41.7)	12 (11.9)	
Left cheek	BCG	18 (47.4)	20 (52.6)	38 (37.6)	0.325
	LCG	12 (50.0)	12 (50.0)	24 (23.8)	
	GCG	9 (33.3)	18 (66.7)	27 (26.7)	
	UCG	6 (50.0)	6 (50.0)	12 (11.9)	
Forehead	BCG	15 (39.5)	23 (60.5)	38 (37.6)	0.006
	LCG	19 (79.2)	5 (20.8)	24 (23.8)	
	GCG	20 (74.1)	7 (25.9)	27 (26.7)	
	UCG	7 (58.3)	5 (41.7)	12 (11.9)	
Chin	BCG	32 (84.2)	6 (15.8)	38 (37.6)	0.770
	LCG	18 (75.0)	6 (25.0)	24 (23.8)	
	GCG	23 (85.2)	4 (14.8)	27 (26.7)	
	UCG	10 (83.3)	2 (16.7)	12 (11.9)	

Table III. Dermatological parameters and *Demodex* species infestation

Factor		Negative (0 to <5) n (%)	Positive (≥5)* n (%)	Total n (%)	*p* value
Skin types	Oily	28 (65.1)	15 (34.9)	43 (42.6)	0.587
	Combination	24 (66.7)	12 (33.3)	36 (35.6)	
	Dry & Sensitive	17 (77.3)	5 (22.7)	22 (21.8)	
Lesion	Positive	54 (70.1)	23 (29.9)	77 (76.2)	0.322
	Non	15 (62.5)	9 (37.5)	24 (23.8)	
Erythema	Positive	59 (69.4)	26 (30.6)	85 (84.2)	0.392
	Non	10 (62.5)	6 (37.5)	16 (15.8)	

*Infestation was defined as having at least five living parasites/cm^2.

Table IV. Distribution body mass index according to cancer groups and infestation

Factor		Underweight* n (%)	Intermediate** n (%)	Overweight*** n (%)	*p* value
Cancer groups	BCG	1 (11.1)	2 (7.7)	35 (53.0)	0.000
	LCG	3 (33.3)	9 (34.6)	12 (18.2)	
	GCG	4 (44.5)	13 (50.0)	10 (15.2)	
	UCG	1 (11.1)	2 (7.7)	9 (13.6)	
Infestation	Positive (≥5)	2 (22.2)	3 (11.5)	27 (40.9)	0.020
	Negative (0–<5)	7 (77.8)	23 (88.5)	39 (59.1)	
Total		**9 (8.9)**	**26 (25.7)**	**66 (65.4)**	

*Underweight < 18.5 kg/m^2, **Intermediate 18.5–24.9 kg/m^2, ***Overweight >25 kg/m^2

by *Demodex* species. Furthermore, both the overweight BMI group (Table IV) and the BCG (Table I) showed a significant association with *Demodex* infestation.

Discussion

This is the first study to investigate the relationship between *Demodex* species infestation and cancer type. Thus far, few reports have addressed *Demodex* species in skin biopsy specimens diagnosed as actinic keratosis and non-melanoma skin cancer (Karaman *et. al.* 2010), the high incidence of demodicidosis in eyelid basal cell carcinomas (Erbagci *et. al.* 2003), and the density of *D. folliculorum* in hematological malignancies (Seyhan *et. al.* 2004). Because of immunosuppression, old age, topical and systemic corticosteroid usage, topical pimecrolimus and tacrolimus usage, and diabetes mellitus are predisposing factors for *Demodex* species incidence (Kulac *et al.* 2008). The increased incidence of *Demodex* species in patients with hematological malignancies, acquired immunodeficiency syndrome (AIDS), and diabetes mellitus suggests that immunosuppression plays a major role (Akilov *et al.* 2004).

Demodex has been detected in immunocompromised children, such as those with acute lymphoblastic leukemia, and caused rosacea and perioral dermatitis in these children (Morras *et al.* 2003). It was also reported that *Demodex* species infestation is more common among those with AIDS and lymphoproliferative disorders (Patrizi *et al.* 1997). In another study, *Demodex* species infestation in facial epidermal neoplasms were investigated and patients with basal cell carcinoma had the highest levels, whereas low levels of infestation were found in those with seborrheic keratosis, trichilemmoma, and squamous cell carcinoma (Sun *et al.* 2005). In the present study, the prevalence of *Demodex* species was high in patients with cancer. This result is similar to that in patients with hematologic malignancies (Seyhan *et al.* 2004). Interestingly, infestation was more frequent in the BCG than in other cancer groups. Although this may be due to breast cancer causing additional immune disturbance of the skin, it may also be coincidental.

The traditional treatment of cancer was represented by pyramid with chemotherapy. These medications have immunosuppressive effects in addition to their immunomodulatory activities. Many studies have shown that treatments increase the rate of infection in patients with cancer (Lau G.K.K. 2008). Although these drugs have immunosuppressive effects, we found no difference in *Demodex* species infestation rates between the chemotherapy-administered and no (initial) chemotherapy group. Chemotherapy agents used in the treatment of cancer may not cause immune disturbance in the skin and/or only immunosuppression with chemotherapy in the facilitation of infestation *Demodex* species could not be suggested. *Demodex* species, like other cutaneous microbes, play different roles depending on host status (Cogen *et al*. 2008). Several factors, such as age, gender, skin type, and presence of lesions and erythema, could allow infestation of *Demodex* species (Lacey *et al*. 2011). Conversely, in our results, infestation of *Demodex* species in patients with cancer did not differ significantly according to dermatological and demographic parameters. Conversely, particular physical characteristics of an individual may influence their infestation status. Our preliminary study showed that patients with cancer have a higher BMI (65.4%). Both an overweight BMI (40.9%) (Table IV) and breast cancer (37.6%) (Table I) showed significant associations with *Demodex* species infestation, indicating that both breast cancer and overweight BMI, which are risk factors for cancer, may be associated with *Demodex* species infestation.

In terms of conclusions, the following question arose: "Are cancers and chemotherapy that could cause a result and/or cause of *Demodex* species infestation?". Results showed that the rate of *Demodex* species infestation was higher in patients with breast cancer. Thus, cancer – and particularly breast cancer – is a risk factor for *Demodex* species infestation.

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