Basal cell carcinoma and demodicidosis: 
Is there an etiologic or coincidental relationship?

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Although solar irradiation is the major factor in the 
development of basal cell carcinoma (BCC), some other factors 
also seem to play an etiopathogenetic role regarding the fact that 
relatively sun-protected areas are also often involved. 
Pilosebaceous follicle mites, Demodex folliculorum and 
Demodex brevis are found most frequently and densely in the 
same facial areas including eyelids, forehead, nasal and 
periauricular regions where basal cell carcinomas also appear 
more commonly than elsewhere. We therefore investigated 
whether there is an etiopathogenetic relationship between 
demodicidosis and BCC. We evaluated a total of 142 
histopathologic skin specimens which include at least 5 
pilosebaceous units, taken from 94 cases with BCC and from 48 
healthy subjects with benign skin lesions. The demodicidosis 
rate and mean demodex number were found significantly higher 
in BCC cases (44.68%, and 0.872±1.193, respectively) than those 
in controls (25%, and 0.458±1.009, respectively) (p<0.05). Mite 
frequency was significantly higher in the periorbitally located 
BCCs as compared to other locations (p<0.05), while it did not 
differ significantly among the histologic subtypes of BCC 
(p>0.05). Conclusively, demodicidosis can be one of the 
predisposing factors which contribute to the carcinogenesis 
process of BCC, by causing perifollicular chronic inflammation 
or by its traumatic effect. Another explanation for these results 
would be that an age-related decline in immunity may be 
responsible for the increased mite positivity and mite numbers in 
BCC cases, or these findings may indicate only a coincidental 
relationship between demodicidosis and BCC, but not an etiologic 

Key words: Basal cell carcinoma, demodicidosis, relationship

Basal cell carcinoma (BCC) is the most common malignancy of the skin. It 
constitutes more than 75% of nonmelanoma skin cancers which account for one 
third of all cancers (1). It appears most commonly in the face, particularly on the
nose, eyelids, medial canthi and periauricular areas (1,2). Although UV radiation is the major factor in the development of BCC, some other factors including genetic predisposition, embryologic abnormalities, carcinogenic stimuli involving various traumas, some congenital malformations such as nevus sebaceous, burns, exposure to inorganic arsenic, immunosuppression, and X-rays were also presumed to play roles in its etiopathogenesis (2-4). Noodleman and Pollack (5) have found a previous trauma history in 7.3% of 1774 BCC lesions which were treated by Mohs surgery. BCC arises mostly over the hair bearing skin areas which are also rich for sebaceous glands, especially on the face, whereas it may very rarely develop in nonfollicular skin (e.g. palms) except in the nevoid basal cell epithelioma syndrome (2-4). Demodex mites parasitize asymptomatically hair follicles, sebaceous glands, eye lashes, and meibomian glands. Two different species are found in humans as being a long form (D. folliculorum) and a short form (D. brevis). D. folliculorum lives in clusters in the small hair ducts, D. brevis is found singly in the depth of sebaceous glands (6-9). When they are found in large numbers and in extrafollicular location, they can be pathogenic and lead to various disorders such as papulopustular and granulomatous rosacea, pityriasis folliculorum, blepharitis, chalasion, perioral dermatitis, and rosacea-like demodicidosis (6-10). Interestingly, these metazoans mostly reside in periorbital, nasal, and periauricular regions where BCC also arise most frequently (1-3,6-8). On the other hand, a relationship between BCC and pilosebaceous follicle is well known, and origin of BCC has been shown to be a cell with pluripotential capacity, located largely in follicular outer root sheath and in epidermis (3,4,11). In addition, BCC is closely associated with and dependent to its surrounding stroma suggesting the presence of some mesodermal factor(s) which functions as intrinsic promoters (3,4). Because of these observations, we investigated whether there is a possible etiopathogenetic relationship between demodicidosis and basal cell carcinoma.

Materials and Methods

This retrospective histopathological study was performed on the skin biopsy specimens taken from the cases with BCC within the last 8 years (from 1992 to 1999). We examined 145 hematoxylin-eosin stained skin tissue slides under light microscopy for the presence of Demodex mites which were located in close proximity to BCC, that is, within or in directly adjacent areas of tumor islands. Of these slides examined, 94 slides which included at least five hair follicles were evaluated. As control, 58 skin biopsy specimens taken from the age-, sex-, and location-matched healthy subjects were examined, and 48 out of those which also included five hair follicles were evaluated. Demodex positivity, the type of mite, and mite numbers in each specimen were noted. In addition, the types of BCC, and the degree of perifollicular and peritumoral inflammation were determined in both groups. For statistical evaluation, two tailed t-tests for independent groups, and chi squared test were used.

Results

Demodicidosis was present in 42 out of 94 BCC cases (44.68%) (Figure 1) and in 12 out of 48 control cases (25%).
Fig 1. A close proximity between tumor islands and pilosebaceous units which contain demodex mites (H&E X40)

The difference was statistically significant (t=2.328, p<0.05). D. folliculorum longus was found positive in 25 cases in BCC group (Figure 2) and in nine cases in control group. While D. brevis was present in 10 of BCC cases (Figure 3) and in two of controls, mixed infestation with both species were seen in seven of BCC cases, and in only one case in control group.
BASAL CELL CARCINOMA and DEMODICIDOSIS

Fig 2. Demodex folliculorum located longitudinally within hair duct and perifollicular moderate infiltration (H&E X100)

Fig 3. D. brevis within sebaceous gland surrounded by a marked lymphocytic infiltration (H&E X100)

These results were not found significantly different ($\chi^2=1.754$, $p>0.05$). Mean mite number was $0.872\pm1.193$ in BCCs and $0.458\pm1.009$ in controls and the difference was statistically significant ($t=2.058$, $p<0.05$). No significant differences in demodicidosis rates were found in various locations of BCC ($p>0.05$) except that in the eyelid BCCs in which mite positivity (72.22%) was significantly higher than those in other areas ($\chi^2=5.504$, $p<0.05$) (Table 1). Demodicidosis frequencies did not also show any significant difference in the solid, morpheaform, adenoid and superficial types of BCC ($\chi^2=1.6$, $p>0.05$) (Table 2)
Table 1
Demodicidosis prevalences and mean mite numbers in various locations in study groups

<table>
<thead>
<tr>
<th>Location</th>
<th>Demodicidosis prevalences</th>
<th>Mean mite numbers</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>BCC cases</td>
<td>Controls</td>
</tr>
<tr>
<td>Periorbital</td>
<td>72.22% (13/18)</td>
<td>0% (0/4)</td>
</tr>
<tr>
<td>Perinasal</td>
<td>44.82% (13/29)</td>
<td>16.66% (2/12)</td>
</tr>
<tr>
<td>Scalp</td>
<td>42.85% (3/7)</td>
<td>0% (0/1)</td>
</tr>
<tr>
<td>Cheeks</td>
<td>40% (6/15)</td>
<td>50% (8/16)</td>
</tr>
<tr>
<td>Periauricular</td>
<td>35.71% (5/14)</td>
<td>0% (0/4)</td>
</tr>
<tr>
<td>Perioral</td>
<td>20% (1/5)</td>
<td>8.33% (1/12)</td>
</tr>
<tr>
<td>Forehead</td>
<td>33.33% (1/3)</td>
<td>8.33% (1/12)</td>
</tr>
<tr>
<td>Neck</td>
<td>0% (0/3)</td>
<td>0% (0/1)</td>
</tr>
<tr>
<td>Overall</td>
<td>44.68% (42/94)</td>
<td>25% (12/48)</td>
</tr>
</tbody>
</table>

\[ t = 2.328, p < 0.05 \]

<table>
<thead>
<tr>
<th>BCC subtypes</th>
<th>Total number</th>
<th>Mite positive cases</th>
<th>Prevalence (%)</th>
</tr>
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<tbody>
<tr>
<td>Solid</td>
<td>57</td>
<td>24</td>
<td>42.10</td>
</tr>
<tr>
<td>Morpheaform</td>
<td>22</td>
<td>12</td>
<td>54.54</td>
</tr>
<tr>
<td>Adenoid</td>
<td>11</td>
<td>4</td>
<td>36.36</td>
</tr>
<tr>
<td>Superficial</td>
<td>4</td>
<td>2</td>
<td>50.0</td>
</tr>
</tbody>
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\[ \chi^2 = 1.6, p > 0.05 \]

In general, the hair follicles and sebaceous glands where D. folliculorum and D. brevis inhabited were located adjacent to the tumor islands, and they often were surrounded by a moderate to marked cellular infiltrate which continued around the tumor nodules. No Demodex granuloma was seen in the dermis in BCC cases as well as in controls.

Of control slides which were evaluated for demodicidosis, 24 cases had melanocytic nevi. The other specimens belonged to hemangioma (three cases), xanthelasma (three cases), acanthoma fissuratum (two cases), fibroepithelioma (five cases), epidermal inclusion cyst (four cases), pyogenic granuloma (two cases), dermoid cyst (two cases), and chalasion (three cases). In control group, histologic examination of five slides belonging to melanocytic nevus revealed only a mild lymphocytic inflammation around infested hair follicles.
Discussion

Because one third of BCCs occur on the skin areas which are relatively less protected, and BCC arises only rarely on the dorsa of hands, other predisposing factors than UV radiation seem to have also some roles for the development of this most commonly seen peculiar skin tumor (2-5,12-14). BCC has been reported to arise in sites of chronic trauma and chronic inflammation including surgical and other scars, leg ulcers, previous varicella lesions, burns as well as on vaccination or venipuncture sites (5,12-14). It is a stroma-dependent tumor, and metastasize very rarely. It has been suggested that some mesodermal intrinsic promoters with other carcinogenic stimuli may lead to BCC development because BCC transplants can survive only when transplantation was done with accompanying peritumoral stroma (2-4). There are some histologic observations favouring this hypothesis: A mixed cellular infiltrate resembling that in type IV hypersensitivity reaction is present near the tumor islands. Peritumoral infiltration is rich in T cells which express activation antigens on their surfaces, and Langerhans cells represent 4% to 15% of the infiltrate (2,4).

Demodex mites are obligatory ectoparasites which inhabit most commonly in the pilosebaceous units of facial and eyelid skin, in eyelashes, eyebrows, and meibomian glands. The mites are found also in domestic animals and they can be pathogenic for them. In dogs, they can cause the potentially lethal generalised demodectic red mange (8). Demodex mites have been shown to present in 84% of 100 normal eyelid skin biopsies, moreover mite positivity has been increased up to 100% of the cases over the age of 70 years (15). By examination of sebum from nasolabial folds, mite frequency has been found as 54.9% in 370 healthy subjects (16). When the mite multiplies and reaches to a sufficient number, it can become pathogenic due to its enhanced irritating action (7-9). Because of consumption of epidermal cells by its own enzymes, Demodex causes breaches in the superficial follicular epithelium which result in follicular distension and keratinization. Occasionally, it can elicit even a true Demodex folliculitis (7-9). In 69 selected biopsies, 986 Demodex were found in 710 follicles, and a statistically significant relationship was established between the presence of Demodex and perifollicular lymphohistiocytic inflammation (17). Demodex mites were observed in 29% of unselected biopsy materials and a chronic lymphocytic infiltration was determined in more than 70% of cases with demodicidosis (18). In our study, five control cases (10.41%) exhibited a mild perifollicular chronic inflammation. In most BCC cases, hair follicles and sebaceous glands harbouring Demodex mites were surrounded by a moderate to marked perifollicular inflammation, however these findings were commented as to be a part of peritumoral host immune reaction.

The host immune defence appears to be the most important factor to prevent mite overgrowth (19,20). Some cases of demodicidosis have been reported in immunosuppression, e.g. in patients under chemotherapy, in children suffering from HIV infection or leukemia, and after topical potent steroid application (8-10). On the other hand, host immune reaction can be modulated by ectoparasites (19-21). The parasites are able to modulate, evade or restrict the host immune response (20). Responses to mitogens are severely depressed in the generalized demodicidosis of dogs and it has been suggested that immunosuppression follows rather than precedes the clinical manifestations of the disease (21). An
impaired blastogenic response of lymphocytes to mitogens has been observed in some cases of BCC, however, only in multiple BCCs (2,4). It is unknown whether there is a relationship between immunosuppression and the increasing prevalence of BCC, but even if it exists, it is not as dramatic as in squamous cell carcinoma development (4).

We found significantly higher results in demodicidosis rate and in mean mite number in BCC cases than those in controls. Our results may be commented in several ways. First, a presumptive immunosuppression created by demodecic infestation that is based on the results of animal studies performed by Barriga et al. (21), may be in favour of cancer development in the aged persons with already poor immunity. Second, an age-related decline in the immune reactivity may have allowed both harbouring of these parasites in the skin and development of BCC simultaneously. Finally, this association can be completely coincidental, due to similar locations which are preferred by both conditions. With further detailed researches, more conclusive results could be obtained in this topic.

References