Differentiating Basal Cell Carcinoma from Trichoepithelioma by Using Androgen Receptor Expression

Yu-Fen Lee  Yun-Ting Chang  Han-Nan Liu

**Background:** To distinguish a basal cell carcinoma (BCC) from a trichoepithelioma (TE) can be difficult even for an experienced dermatopathologist.

**Objective:** In this study, we sought to reconfirm the androgen receptors (AR) immunostaining pattern of BCC and TE and to determine whether AR immunoreactivity could serve as a useful maker to differentiate these two tumors.

**Methods:** Twenty-one cases of circumscribed BCC, solid type and nineteen cases of TE were obtained from the files of the Department of Dermatology, Taiwan. The patients’ medical records were reviewed for the clinical manifestations including age, gender, anatomic sites, color and personal history, especially on the associated AR-related malignancy. The formalin-fixed, paraffin-embedded specimens with immunohistochemical staining for androgen receptor expression were surveyed.

**Results:** Our study revealed that AR expression was present in 52.4% circumscribed BCC, solid type. On the other hand, none of the 19 TE samples disclosed any nuclear AR expression. The AR expression in BCC was detected as clusters or scattered individual tumor cells and showed great variations in intensity. In addition, three patients in the AR-positive BCC group had other AR-related malignancies.

**Conclusion:** In conclusion, when we deal with conflicting cases, besides the clinical presentations and the histopathological criteria, AR immunohistochemical staining could give more information for the diagnosis. A positive AR stain could significantly push the diagnosis toward BCC. (Dermatol Sinica 27: 154-160, 2009)

Key words: Basal cell carcinoma, Trichoepithelioma, Androgen receptor

**INTRODUCTION**

Basal cell carcinoma (BCC), which is derived from nonkeratinizing cells that originates in the basal layer of the epidermis, is the most common malignant skin cancer in human beings. Trichoepithelioma (TE) is a benign skin tumor showing differentiation toward hair and hair follicles, especially follicular germs. It is most commonly found on the face and may occur as a solitary non-familial or multiple-familial type. Distinguishing BCC from TE can be difficult even for an experienced dermatopathologist. So a number of immunohistochemical studies, 

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In the normal skin, the expression of androgen receptors (AR) could be identified in basal and differentiating sebocytes in sebaceous glands, pilosebaceous duct keratinocytes, interfollicular epidermal keratinocytes, dermal fibroblasts, luminal epithelial cells of apocrine glands in genital skin, and in certain cells of the secretory coils of eccrine sweat glands in all body sites.\(^{11-15}\) Besides, many benign and malignant skin tumors also expressed the staining of AR, such as chondroid syringoma, sebaceous nevi, sebaceous hyperplasia, sebaceous adenoma, sebaceous epithelioma, sebaceous carcinoma and benign and malignant sweat gland neoplasms.\(^{13-16}\) On the other hand, there was no immunoreactivity evident in the outer root sheath of hair follicles,\(^{14,16}\) the basal keratinocytes beneath the follicular infundibulum or in the inner root sheath, germinative matrix, hair shaft, hair bulb,\(^{15}\) eccrine glands or ducts and the keratinocytes in the normal skin.\(^{15}\)

Recent investigations stated that BCC also showed positivity for AR immunoreactivity. The AR expression was present in approximately 60 to 78% of BCC cases.\(^{14,17,18}\) However, no AR expression was observed in hair follicle tumors,\(^{13}\) especially benign trichoepitheliomas and trichoblastomas.\(^{17,18}\) Accordingly, this study was undertaken to reconfirm the AR immunostaining pattern of BCC and TE and to determine whether AR immunoreactivity could serve as a useful maker to differentiate these two tumors.

**MATERIAL AND METHOD**

Twenty-one recent cases of circumscribed BCC, solid type and nineteen cases of TE were obtained from the files of the Department of Dermatology, Taipei Veterans General Hospital, Taiwan. All the BCC cases showed basoloid tumor islands with peripheral palisading, at least focal retraction artifact and no papillary mesenchymal bodies and two of the three additional histopathological findings: mucinous or fibromucinous stroma, at least focal mitotic figures and melanin deposition. On the other hand, all the TE showed basoloid tumor islands with peripheral palisading and papillary mesenchymal bodies and two of the three additional histopathological findings: well-formed horn cysts, fibrous or fibromucinous stroma and no retraction artifact. The BCC cases were diagnosed in 2004 and 2005 and the TE cases were diagnosed from 1980 to 2007. The patients’ medical records were reviewed for the clinical manifestations including age, gender, anatomic sites, color and personal history, especially on the associated AR-related malignancy. To perform immunohistochemical staining of AR, serial 5-μm thick sections were prepared from formalin-fixed, paraffin-embedded blocks. The slides were deparaffinized in xylene thrice for 5 minutes and rehydrated through graded ethanol solutions to distilled water. Antigen retrieval was carried out by heating the sections in 10mM ethylenediamine-tetraacetic acid (PH 9.4) for 10 minutes. Then the sections were incubated in 3% hydrogen peroxide to inactivate endogenous peroxidase activity. Tissue sections were then treated at 4°C with a mouse anti-human monoclonal antibody (diluted 1:50) to human AR (Clone AR441, DakoCytomation, Carpinteria, California, USA) and were subsequently incubated in EnVision\(^{\text{+}}\) Dual Link System-HRP (DakoCytomation) for 30 minutes at room temperature. Finally, the immunoreactive signal was detected.
with chromogen 3-amino-9-ethyl carbazole (DakoCytomation) and the sections were then counterstained with Mayer’s Hematoxylin. Benign prostate gland tissue served as a positive control for AR. Besides, normal sebocytes within sebaceous glands were used as the internal positive control. Any nuclear staining of AR was interpreted as positive. Furthermore, the field of the tumor mass, which expressed the AR most strongly, was selected. The amount of the AR positive cells was counted under the high power field.

RESULTS

Using the sebocytes within sebaceous glands as a positive internal control, AR expression was present in 11/21 (52.4%) circumscribed BCC, solid type. The nuclear staining of AR was present in a single cell or a nest of cells of the BCC tumor mass (Fig. 1A, 1B, 1C). The amount of AR-positive cells per high power field showed significant variations from 5 to 271. There were no unique clinical characteristics of the BCC samples showing positive AR staining (Table 1). In addition, there were no BCC lesions that exhibited sebaceous differentiation. Based on the expression of AR, AR-positive group and AR-negative group were analyzed. In the AR-positive BCC group, the male-female ratio was 10:1, the average age was 75.9 years and 81.8% (9/11) tumor was located on head and neck regions. In the AR-negative BCC group, the male-female ratio was 7:3, the average age was 68.4 years and 70% (7/10) tumor was located on head and neck regions (Table 2). The AR positivity rates in male and female patients with BCC were 58.8% and 25%, respectively. However, the sample size was too small to reach a statistically definite conclusion. With regards to TE, all the 19 samples disclosed negative nuclear AR expression (Fig. 1D). The number of cases with statistically significant positive AR expression was higher for BCC compared to trichoepithelioma (χ2 test, P<0.001). Three of the 11 AR-positive BCC cases had other AR-related malignancies. They were invasive ductal carcinoma of breast, brain tumor at left cavernous sinus, and carcinoma of prostate, respectively.

DISCUSSION

In the present study, we examined 21 BCC and 19 TE samples for AR expression to see the AR immunostaining pattern of BCC and TE and if this maker might aid in the differentiation between the two tumors. The AR positivity was seen in 52.4% of BCC while there was no AR expression in TE. The AR expression in BCC was detected as clusters or scattered individual tumor cells and showed great variations in intensity. The previous studies showed that the AR expression was present in approximately 60 to 78% of BCC cases. However, no AR expression was observed in hair follicle tumors, especially benign trichoepitheliomas and trichoblastomas. Our study supported the previous finding that AR immunoreactivity
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could serve as a useful maker to differentiate BCC and TE. Besides, there was no race differences between the Westerns and the Taiwanese.

In clinical practice, differentiation between BCC and TE histopathologically may be difficult or even impossible, especially in small specimen. Many immunostains had been tried to enable distinction among them. Bcl-2 may be of some value in distinguishing BCC from TE. Bcl-2 stained BCC in a diffuse pattern, whereas TE showed staining of the outermost epithelial layer. TGF-beta staining pattern appears to be a helpful additional marker together with bcl-2 in differentiating between TE and BCC. Conden-
sation of CD10-positive stromal cells around basaloid nests was statistically significant in differentiating TE from BCC. Conversely, CD10-positive basaloid cells were seen predominanty in BCC. The spindle-shaped cells surrounding the islands of TE cells were focally strongly positive for CD34. In BCC, the spindle-shaped cells surrounding the nests of tumor cells were CD 34 negative. Ki67 and PCNA labeling were noted with significantly increased numbers and the patterns were recognizably different in BCCs compared to TEs. Merkel cells were found in association with TE but not in BCC. However, the opinions varied in the literature.

These immunohistochemical studies were not so reliable as AR.

As in the previous studies, the AR expression of BCC in the present study was conducted in clusters or scattered individual tumor cells. So any nuclear staining of AR was interpreted as positive. Eleven of the twenty-one (52.4%) BCC cases showed AR positivity and none of the TE cases showed AR expression in our study. Although the positive rate of our results was lower than that of other studies (varied from 60% to 78%), AR was still a reliable marker in distinguishing the two types of tumors. There were no unique clinical characteristics of the BCC samples showing positive AR staining. It was unclear why AR expressed in some cases of BCC rather than others. The demonstrated staining differences may relate to the distinct origin and biological behavior of the two tumors and may therefore be of value in subsequent patient management.

AR belong to the nuclear receptor fam-

### Table 1 The Characteristics of the AR-Positive BCC Cases

<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>Gender</th>
<th>Location</th>
<th>The amount of AR-positive cells per high power field</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>76</td>
<td>Male</td>
<td>Right eyebrow</td>
<td>216</td>
</tr>
<tr>
<td>2</td>
<td>86</td>
<td>Male</td>
<td>Left nasal ala</td>
<td>271</td>
</tr>
<tr>
<td>3</td>
<td>74</td>
<td>Male</td>
<td>Right shoulder</td>
<td>143</td>
</tr>
<tr>
<td>4</td>
<td>81</td>
<td>Male</td>
<td>Right upper lip</td>
<td>98</td>
</tr>
<tr>
<td>5</td>
<td>75</td>
<td>Male</td>
<td>Nose</td>
<td>6</td>
</tr>
<tr>
<td>6</td>
<td>76</td>
<td>Male</td>
<td>Nose</td>
<td>30</td>
</tr>
<tr>
<td>7</td>
<td>82</td>
<td>Female</td>
<td>Right nasal ala</td>
<td>16</td>
</tr>
<tr>
<td>8</td>
<td>74</td>
<td>Male</td>
<td>Nasal root</td>
<td>10</td>
</tr>
<tr>
<td>9</td>
<td>47</td>
<td>Male</td>
<td>Left nasal bridge</td>
<td>101</td>
</tr>
<tr>
<td>10</td>
<td>82</td>
<td>Male</td>
<td>Right chest</td>
<td>19</td>
</tr>
<tr>
<td>11</td>
<td>82</td>
<td>Male</td>
<td>Right nasal ala</td>
<td>5</td>
</tr>
</tbody>
</table>

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ily of transcription factors, and these nuclear receptors control transcription by the recruitment of a variety of co-activators and co-repressors. They mediate the biological actions of physiological androgens such as testosterone and 5-α-dihydrotestosterone. They are essential for differentiation, development and maintenance of the male reproductive organs. The patients with BCC included 17 males and 4 females in our study. At least half of the BCC could show nuclear AR expression in the present and other studies. Since we knew that the androgen concentration was higher in males than females, is the interaction between androgen and AR act as one of the etiologies to develop BCC? A previous clinicopathological analysis of 86 BCC cases in Taiwan showed a male-female ratio of 1.15:1.50. In Westerns, 57% BCC cases were men. BCC was not so prevalent in the male. The male predominance (17/21, 81%) in our study may be due to the fact that majority of the patients visiting our hospital are retired veterans. Besides, the BCC cases were not randomly selected, so they couldn’t represent the real condition.

Besides the skin neoplasm, a number of visceral tumors also express the nuclear staining of AR. They included benign prostate hyperplasia, adenocarcinoma of the prostate, breast carcinoma, ovarian carcinoma, adenomyosis, external endometriosis, endometrial adenocarcinoma and meningioma. In present study, three patients in the AR-positive BCC group had other AR-related malignancies: invasive ductal carcinoma, meningioma and carcinoma of prostate. But none of the AR-negative BCC group had the associated malignancy. This had not been noted before. So, it may be interesting to know if the androgen and AR interaction play important roles in the development of BCC and these tumors. Besides, hormonal therapy is one of the treatment choices of these tumors. Whether hormonal therapy could be the potential treatment of BCC needs further evaluation and investigation.

In conclusion, it is not very easy to differentiate BCC from TE by clinical presentations and histopathological criteria alone. AR immunohistochemical staining could give more information for the diagnosis. A positive AR stain could significantly push the diagnosis toward BCC. Undoubtedly, regular follow-up is necessary for these conflicting cases.

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利用雄性賀爾蒙接受器來鑑別診斷基底細胞癌跟毛髮上皮瘤

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背景：要區別基底細胞癌跟毛髮上皮瘤對有經驗的皮膚病理學者來說也有相當的難度。
目的：在本研究中，我們試圖確認基底細胞癌跟毛髮上皮瘤雄性賀爾蒙接受器的免疫染色型態，以及雄性賀爾蒙接受器的表現是否可以用來鑑別診斷基底細胞癌跟毛髮上皮瘤。
方法：我們從皮膚部的檔案中選取了二十一位基底細胞癌和十九位毛髮上皮瘤的病例，檢閱病人的病歷以獲得臨床表現資訊，包括年齡、性別、病灶位置、顏色以及個人病史，尤其是是否有雄性賀爾蒙接受器相關的腫瘤。並且我們也藉由免疫組織染色，檢視雄性賀爾蒙接受器在福馬林固定、石蠟包埋的檢體內的表現。
結果：我們的研究發現百分之52.4的基底細胞癌會表現雄性賀爾蒙接受器，而毛髮上皮瘤則不會有任何雄性賀爾蒙接受器的表現。在基底細胞癌中，雄性賀爾蒙接受器會以成群或單個表現存在而且強度不一。此外，有三位表現雄性賀爾蒙接受器的基底細胞癌病人也有其他雄性賀爾蒙接受器相關的腫瘤。
結論：總結來說，當我們遇到困難診斷的病例時，除了臨床表現和組織病理的準則以外，雄性賀爾蒙接受器的免疫染色可以提供更多的資訊。若有雄性賀爾蒙接受器的表現，則診斷較趨近於基底細胞癌。（中華皮誌：27: 154-160, 2009）