The role of protein-53 amyloid in determining the aggressiveness of basal cell carcinoma regulated by interleukin-6, myeloid cell leukemia-1 and basic fibroblast growth factor

Prasetyadi Mawardi,1 Handono Kalim,2 Kusworini Handono Kalim,3 Loeki Enggar Fitri,4 Karyono Mintarjo,4 Ambar Mudigdo,4 Oyong Oyong,4 Brian Wasita4
1Dermatovenereology Department, Medical Faculty of Sebelas Maret University/Dr. Moewardi Public Hospital, Surakarta; 2Internal Medicine Department, Faculty of Medicine Brawijaya University/dr. Saiful Anwar Public Hospital, Malang; 3Clinical Pathology Department, Faculty of Medicine Brawijaya University/dr. Saiful Anwar Public Hospital, Malang; 4Parasitology Department, Faculty of Medicine Brawijaya University/dr. Saiful Anwar Public Hospital, Malang; 5Pathology Department, Faculty of Medicine, Brawijaya University/dr. Saiful Anwar Public Hospital, Malang; 6Pathology Department, Medical Faculty of Sebelas Maret University/Dr. Moewardi Public Hospital, Surakarta, Indonesia

Abstract

Basal cell carcinoma (BCC) is a common malignant skin tumor that rarely metastasizes, even though it is often locally aggressive. Several factors, like a large size (more than 3 cm), face localization, exposure to ultraviolet rays, histological variants, infiltration level and perineural or perivascular invasion, are associated with a more aggressive clinical course. However, it rarely metastasizes. BCC can cause significant damage due to its local and aggressive recurrences. The p53 gene is activated upon the induction of DNA damage to either arrest the cell cycle or to induce apoptosis. When mutated, p53 is no longer able to properly accomplish these functions. Apparently, appropriate p53 functioning is crucial for the suppression of tumor development. The p53 gene is not reactive in cells where DNA is undamaged. When there is DNA damage, the gene suspends the cell cycle until the damage can be repaired. The p53 gene is not reactive in cells where DNA is undamaged. When there is DNA damage, the gene suspends the cell cycle until the damage can be repaired. If there is a mutation in p53, the cell cycle continues unrestrained and damaged DNA is reproduced, leading to uncontrolled cell proliferation and cancerous tumors. The existence of amyloid deposits in BCC has been found in previous studies. The frequency of secondary amyloidosis in BCC varies from 50% to 75% in the literature. In the past, the origin of amyloid in BCC was thought to be derived from degenerated epithelial cells following apoptosis. This study aimed to investigate the differences in the immunohistochemical expression of p53, amyloid deposits, IL-6, MCL-1 and bFGF in aggressive BCC. The expression of these markers was associated with clinicopathological features such as age, gender and anatomical sites of the lesions, as well as aggressive vs non-aggressive forms of BCC.

Materials and Methods

Archived specimens from 51 cases diagnosed with primary BCC were collected from December 2014 to May 2016 at the Dr. Moewardi Public Hospital in Surakarta, Central Java, Indonesia. Clinical findings such as age, gender and tumor localization were obtained from medical records. Specimens were reevaluated independently by two expert pathologists who agreed on all specimens involved in the study. Histopathological types of BCC were determined and histopathological classification of the lesions was performed according to the criteria proposed by Dixon and Jacobs et al. In order to detect p53 protein expression in BCC specimens, we performed immunohistochemical staining as follows. Initially, we chose adequately represented BCC paraffin blocks, and then the blocks were deparaffinized and dehydrated. Strongly positive control slides were used in each run of the immunohistochemical staining procedure for each protein, i.e. p53 (breast carcinoma), IL-6 (tonsil) and bFGF (brain tissue). Expression measurement of p53, IL-6, MCL-1, and bFGF and p53 amyloid used J-Image (open access). Amyloid deposits were assessed with the Congo Red staining procedure. Statistical analyzed with Kruskal Wallis and Mann Whitney method for comparing data, and Pearson’s chi square for correlation studied.

Results

From the 51 BCC pathologic's slides that underwent histopathological examinations, thirteen patients were excluded. In this study we found predominantly females than males (55.3%; 44.7%). The age range of the patients were 41-90 years old, with the most common occupation was farmer (53.6 %) and housewife (26.7 %). According to the duration of illness, most patients had symptom for more than 3 years.
Total                      38                   29 (76.3%)                   34 (89.4%)                        25 (65.8%)                          34 (89.4%)                          25 (65.8%)                  34 (89.4%)

Table 1. Protein 53 expression, Amyloid deposite, p53amyloid, IL-6, MCL-1 and bFGF related BCC aggressivity.

Discussion

Basal cell carcinoma is the most common cutaneous cancer, with increasing prevalence especially in lighter skinned individuals or in the Caucasian population. Several studies have shown that BCC is more often found in men compared to women. This may reflect a higher rate of sun exposure in males because of their employment pattern. However, in this study, BCC was found more often in women than in men, i.e. 55.3% vs. 44.7%, respectively. The incidence in women is increasing due to changing fashions in clothing and increased time spent outdoors for recreational or occupational reasons. Based on occupation, this study found that farmers are more frequently affected BCC than others. UV radiation, especially UVB, is responsible for the majority of cutaneous damage and is believed to be the primary risk factor driving tumorigenesis in BCC. In BCC, the origin of amyloid deposits is thought to be derived from degenerated epithelial cells via apoptosis. If the correlation between p53 expression and amyloid obtained a statistically

<table>
<thead>
<tr>
<th>Type</th>
<th>N</th>
<th>P53</th>
<th>Amyloid</th>
<th>p53amyloid</th>
<th>IL-6</th>
<th>MCL-1</th>
<th>bFGF</th>
</tr>
</thead>
<tbody>
<tr>
<td>A BCC</td>
<td>25</td>
<td>18 (47.4 %)</td>
<td>23 (60.5%)</td>
<td>16 (42.1%)</td>
<td>23 (60.5%)</td>
<td>17 (44.7%)</td>
<td>22 (57.9%)</td>
</tr>
<tr>
<td>NA BCC</td>
<td>13</td>
<td>11 (28.9%)</td>
<td>11 (28.9%)</td>
<td>9 (23.7%)</td>
<td>11 (28.9%)</td>
<td>8 (21.1%)</td>
<td>12 (31.5%)</td>
</tr>
<tr>
<td>Total</td>
<td>38</td>
<td>29 (76.3%)</td>
<td>34 (89.4%)</td>
<td>25 (65.8%)</td>
<td>34 (89.4%)</td>
<td>25 (65.8%)</td>
<td>34 (89.4%)</td>
</tr>
</tbody>
</table>

This study also found a close correlation between p53 amyloid with bFGF (p = 0.051) and contingency coefficient (cc) 0.45.

Figure 1. Deposits value of p53 amyloid related to BCC aggressivity.
significant difference, it means there is a difference in the role of p53 in determining the aggressiveness of A BCC and NA BCC (p<0.05). Amyloid fibril deposition has been described in patients with malignant disease. It is more frequently seen in hematological neoplasms and has also been noted in patients with solid tumors. This study also found higher IL-6, MCL-1 and bFGF expression in A BCC than in NA BCC. Pro-inflammatory cytokines induce angiogenesis. The Bcl-2 protein family, including MCL-1, is critical to the regulation of the intrinsic apoptotic pathway and the elimination of cells affected by oncogenic mutations in various human tissues, including the epidermis. Enhancing IL-6 expression also induced MCL-1 expression. MCL-1 is an anti-apoptotic protein that is essential for the survival of multiple cell lineages and is highly amplified in human cancer. Under physiological conditions, the MCL-1 expression is tightly regulated at multiple levels, involving transcriptional, post-transcriptional and post-translational processes. Beta-FGF or FGF-type 2 is the most important angiogenic factor, along with VEGF, and stimulates angiogenesis, which is a sequence of cellular events comprising vascular initiation, formation, maturation, remodeling, and regression, which are tightly controlled to meet tissue requirements. Angiogenesis has an important role in the development and progression cancer.

Conclusions

Given the results of this study, a mid-face location of BCC is significantly more aggressive than BCC at other sites. This study also found BCC more frequently in females than in males. The expression of p53 amyloid was significantly different in A BCC and NA BCC, but was associated with amyloid deposits; p53 amyloid role in determining aggressiveness between A BCC vs. NA BCC was significantly different. The expression of MCL-1 and bFGF was significantly higher in A BCC than in NA BCC.

References