BREAST CANCER AND BASAL CELL CARCINOMA IN THE SAME PATIENT - IS IT RANDOM? (CASE SERIES REPORTS)

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BREAST CANCER AND BASAL CELL CARCINOMA IN THE SAME PATIENT - IS IT RANDOM? (CASE SERIES REPORTS) (Abstract): Non-melanoma skin cancer, including basal cell carcinomas and squamous cell carcinomas, is the most common cancer affecting white-skinned individuals and its incidence is increasing worldwide. Several studies have reported that individuals diagnosed with non-melanoma skin cancer are at higher risk of subsequent or prior diagnoses of second primary malignancies. We report a series of five cases with concomitant basal cell carcinoma and breast cancer; in two cases the basal cell carcinoma was diagnosed after the breast cancer and in three cases it preceded it. Considering the high frequency and low mortality of basal cell carcinomas, they offer an excellent opportunity to study the factors that put some individuals at increased risk of multiple malignancies.

Keywords: BREAST CANCER, BASAL CELL CARCINOMA, NON-MELANOMA SKIN CANCER, MULTIPLE MALIGNANCIES.

Non-melanoma skin cancer (NMSC) is the most common cancer affecting white-skinned individuals and its incidence is increasing worldwide (1). The two major types of NMSC, basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), have a relatively small impact on mortality but their public health impact is considerable. Although they share many similarities, they have different incidence rates and important etiological differences (2, 3).

In comparison with other malignancies, information regarding the incidence of NMSC and BCC is limited due to poor registration practice in most of countries, including Romania (4). The incidence rate appears to be higher compared with other malignancies and it is increasing. Worldwide the incidence of NMSC varies widely with the highest rates in Australia (>1,000/100,000 person-years for BCC) and the lowest rates in parts of Africa (<1/100,000 person-years for BCC) (1). Although the reason for this is unclear, in some countries it may be linked to increased sun-seeking behaviors and improved registration procedures (1).

Several studies have reported that indi-
individuals diagnosed with BCC are at higher risk of subsequent or prior diagnoses of second primary malignancy by about 20-60% (5).

In 2012, the estimated age-adjusted annual incidence of breast cancer in 40 European countries was 94.2/100,000 and the mortality 23.1/100,000, with rather decreased values for Romania: significantly lower incidence of 66.2/100,000 and similar mortality of 21.6/100,000 (6), possibly due to delay in or avoidance of seeking medical attention and advanced stage at diagnosis. Since breast cancer is the most frequently diagnosed non-cutaneous cancer among women, it is not surprising that many individuals with breast cancer will associate BCC.

During a prospective study on breast cancer comprising of 65 patients, we identified 8 patients that associated multiple malignancies, of which 5 (7.7% of all cases) associated basal cell carcinomas. We present the particularities of these 5 patients.

**CASES REPORTS**

**Case 1.** Female patient, aged 77, was diagnosed with malignant tumor of the left mammary gland in September 2013, which was surgically removed (superior-external quadrantectomy with lymphadenectomy -13 lymph nodes) and morphopathological examination revealed an invasive carcinoma of the mammary gland with mucinous areas, stage pT2N0G1 (tab. I). The patient received subsequent radiotherapy and is now continuing treatment with hormone therapy (Tamoxifen).

In July 2015, the patient underwent surgical removal of a white nuanced frontal lesion with central ulceration, which appeared one year before surgery. The anatomo-pathological examination revealed that the lesion measuring 0.7/0.6/0.1 cm was a superficial multicentric basal cell carcinoma and confirmed the excision was in the healthy tissue in all plans (tab. II).

**Case 2.** Female patient, aged 69, was diagnosed with malignant tumor of the right mammary gland in December 2004. Subsequent surgery (Madden modified radical mastectomy, including lymphadenectomy of 8 lymph nodes) followed by the morpho pathological examination identified NOS invasive ductal carcinoma, stage pT1cN2aMxG3 (7 lymph nodes with metastases, 2 lymph nodes > 2cm) (tab. I). The treatment included chemotherapy and radiotherapy, followed by hormone therapy (3 years with Tamoxifen and 2 years of Letrozole).

In September 2015 the patient underwent surgery for a white skin lesion in the nasal region, which appeared 3 years earlier and in the absence of clinical improvement the patient sought medical attention. Surgery was performed and morpho pathological examination revealed a lesion measuring 0.7/0.6 cm corresponding to a superficial multicentric basal cell carcinoma. The examination also confirmed the excision was made in healthy tissue in all the plans (tab. II).

**Case 3.** Female patient, aged 77, was diagnosed with malignant tumor of the right mammary gland in December 2009 when surgery was performed (Madden modified radical mastectomy, including lymphadenectomy of 7 lymph nodes). The morphopathological examination identified NOS invasive ductal carcinoma, stage pT1bN0MxG2 (tab. I). The treatment included chemotherapy followed by hormone therapy (5 years of Letrozole).

In this case, the history of skin lesions preceded the diagnosis of mammary gland tumor. From patient’s data, the first skin lesion appeared around the age of 22
(1968), after a severe sunburn, under the form of a pigmented asymmetrical lesion localized in the left suprascapular region that began to ulcerate and was surgical removed in 2004. The morphopathological examination confirmed a basal cell carcinoma. Four years later, in the proximity of the first lesion, in the posterior cervical region, another lesion appeared and was rapidly surgically removed. The morphopathological examination revealed another lesion of basal cell carcinoma, and confirmed the surgery was performed within oncological safety limits (tab. II).

**TABLE I**

Details on the onset and morphopathological examination of the mammary gland tumor

<table>
<thead>
<tr>
<th>Mammary gland tumor</th>
<th>Year of diagnosis</th>
<th>Estrogen Receptor</th>
<th>Progesterone Receptor</th>
<th>HER 2-neu</th>
<th>Ki67</th>
<th>Ellis-Elston score</th>
<th>Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1</td>
<td>2013</td>
<td>95%</td>
<td>&lt;1%</td>
<td>2+</td>
<td>5%</td>
<td>4</td>
<td>pT2 N0 Mx-G1</td>
</tr>
<tr>
<td>Case 2</td>
<td>2004</td>
<td>NE</td>
<td>NE</td>
<td>9%</td>
<td>3</td>
<td>2</td>
<td>pT1 cN2a Mx-G3</td>
</tr>
<tr>
<td>Case 3</td>
<td>2009</td>
<td>90%</td>
<td>1-2%</td>
<td>2+</td>
<td>11%</td>
<td>2</td>
<td>pT1b N0 Mx-G2</td>
</tr>
<tr>
<td>Case 4</td>
<td>2006</td>
<td>25%</td>
<td>35%</td>
<td>NC</td>
<td>NE</td>
<td>1</td>
<td>pT2 N2a Mx-G1</td>
</tr>
<tr>
<td>Case 5</td>
<td>2013</td>
<td>80%</td>
<td>80%</td>
<td>1+</td>
<td>20%</td>
<td>6</td>
<td>pT2m N2a Mx-G2</td>
</tr>
</tbody>
</table>

(NE - not evaluated, NC - inconclusive)

**TABLE II**

Details on the onset and morphopathological examination of the skin lesion

<table>
<thead>
<tr>
<th>Basal cell carcinoma</th>
<th>Year of clinical onset*</th>
<th>Year of surgical intervention</th>
<th>Size</th>
<th>Characteristics</th>
<th>Localization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1</td>
<td>2014</td>
<td>2015</td>
<td>0.7/0.6/0.1 cm</td>
<td>superficial, multicentric</td>
<td>Face (nasal region)</td>
</tr>
<tr>
<td>Case 2</td>
<td>2012</td>
<td>2015</td>
<td>0.7/0.6 cm</td>
<td>superficial, multicentric</td>
<td>Face (frontal region)</td>
</tr>
<tr>
<td>Case 3</td>
<td>1968 (?)</td>
<td>2004</td>
<td>0.7/0.5 cm</td>
<td>superficial, multicentric</td>
<td>Left suprascapular region</td>
</tr>
<tr>
<td></td>
<td>2008</td>
<td>2008</td>
<td>0.5/0.5 cm</td>
<td>superficial, multicentric</td>
<td>Posterior cervical region</td>
</tr>
<tr>
<td>Case 4</td>
<td>2003</td>
<td>2015</td>
<td>0.9/0.9/0.4 cm</td>
<td>solid, with pigmented areas</td>
<td>Posterior cervical region</td>
</tr>
<tr>
<td>Case 5</td>
<td>2001</td>
<td>2013</td>
<td>1/0.8 cm</td>
<td>solid, with ulcerative areas</td>
<td>Face (temporal region)</td>
</tr>
</tbody>
</table>

(*approximately)

**TABLE III**

Time between the diagnosis of breast cancer and onset of BCC

<table>
<thead>
<tr>
<th>Date of birth</th>
<th>Year of breast cancer diagnosis</th>
<th>Onset of BCC*</th>
<th>Radiotherapy for breast cancer</th>
<th>BCC vs. breast cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1</td>
<td>1938</td>
<td>2013</td>
<td>2014</td>
<td>Yes</td>
</tr>
<tr>
<td>Case 2</td>
<td>1946</td>
<td>2004</td>
<td>2012</td>
<td>Yes</td>
</tr>
<tr>
<td>Case 3</td>
<td>1938</td>
<td>2009</td>
<td>1968</td>
<td>Yes</td>
</tr>
<tr>
<td>Case 4</td>
<td>1953</td>
<td>2006</td>
<td>2003</td>
<td>No</td>
</tr>
<tr>
<td>Case 5</td>
<td>1950</td>
<td>2013</td>
<td>2001</td>
<td>Yes</td>
</tr>
</tbody>
</table>

* presumed
Case 4. Female patient, aged 62, known with malignant tumor of the left mammary gland that was surgically removed in August 2006 (Madden modified radical mastectomy, including lymphadenectomy of 19 lymph nodes) followed by the morphopathological examination that identified invasive tubular carcinoma, stage pT2N2aMx-G1 (7 lymph nodes with metastases) (tab. I), underwent chemotherapy and afterwards hormone therapy (3 years Letrozole, 1 year Tamoxifen and is currently on 6-month treatment with Exemestane).

In November 2015 the patients underwent surgery for a skin lesion localized in the nasal region that appeared approximately 12 years before. The morphopathological examination revealed a lesion corresponding to a solid ulcerative basal cell carcinoma, with pigmented areas (fig. 1). The examination also confirmed the excision was made in healthy tissue in all plans (tab. II).

Case 5. Female patient, aged 65, diagnosed with malignant tumor of the left mammary gland and operated in January 2013 (Madden modified radical mastectomy, including lymphadenectomy of 33 lymph nodes) and the morphopathological examination identified NOS invasive ductal carcinoma, stage pT2mN2aMxG2 (tab. I). The treatment included chemotherapy and radiation therapy followed by hormone therapy (Letrozole).

The patient reported in 2001 a pathological skin lesion located on the face (left temporal region) that was surgically removed simultaneously with the breast lesions. The morphopathological examination confirmed a solid basal cell carcinoma with an ulcerative area (tab. II).
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**DISCUSSION**

We presented five cases associating two primary malignancies: BCC and breast cancer. Considering that our ongoing research included 68 patients with breast cancer, this association was met in 7.4% of the patients. This raised the question of possible underlying mechanisms that lead to this condition.

BCC seems to form in the epidermal stem cells of the outer root sheet of the hair follicle, but the precise origin of BCC it is still unknown. The lesions are classified into five types: nodular-ulcerative, pigmented, sclerodeiform or fibrosing, superficial and fibroepithelioma. Apart from the environmental exposure and immunosuppressive therapy, people with a fair skin type-I complexion (red or blonde hair, light colored eyes, freckles), and those with a history of intermittent sun exposure, especially ultraviolet (UV) - B radiation and severe sunburn during childhood, are at highest risk (7). The treatment options are focused on local control and include mainly surgical techniques. Nonsurgical approaches comprise of radiotherapy, topical injection therapy and photodynamic therapy (8, 9).

Regarding breast cancer, this is a heterogeneous disease with histological differences within tumors and between patients. The cancer development in the normal mammary gland depends on stem cells,
neighboring cells including fat cells and fibroblasts that play distinct roles through specific signaling pathways (10). Endogenous hormones (sex hormones, growth hormone axis), reproductive factors (lower parity, older age at first giving birth, younger age at menarche, older age at menopause), oral contraceptives and hormone replacement therapy, family history and genetic factors (BRCA1 and BRCA2 mutations), alcohol and smoking, diet, overweight and obesity are known to be risk factors in breast cancer (11). The treatment of breast cancer includes surgery, radiation therapy, chemotherapy, and hormone therapy and the prognosis and selection of therapy may be influenced by clinical and pathological features.

It is likely that the association of BCC and other cancers may have an etiologic link. The deficiencies of pathways responsible for protecting against cellular transformation in multiple tissues, such as DNA repair (e.g.: nucleotide excision repair - NER - pathway) (12,13,14) or immune responses (e.g.: UV-induced immunosuppression) (15,16), may play a role in cutaneous and internal carcinogenesis.

The major environmental cause of BCC is exposure to solar UV radiation (17, 18). The individual risk appears to be determined largely by cumulative exposure to solar radiation, in combination with individual susceptibility. Thus, it is important to realize that BCC incidence is based on a lifetime of exposure to risk factors, and the older population that is currently being diagnosed used very little sun protection and received very little education regarding the effects of ultraviolet radiation (UV) (19). On the other hand, the exposure to UV-B radiation is necessary to provide sufficient vitamin D, known to reduce the risk of cancer incidence, but data considering this issue are conflicting (19,20).

Breast cancer after BCC

In addition to having an increased risk for new skin cancer, patients with basal-cell carcinoma are at increased risk for non-cutaneous cancer at various sites.

In one of the largest prospective cohort study on topic (18) (performed in U.S.A.; included 107339 women, 46237 men), the researchers found that among patients with a personal history of NMSC (without specification to BCC or SCC) there was an increased risk of subsequent malignancies, specifically breast (RR = 1.19; 95% CI 1.11-1.28, p<0.0001; AR = 87 per 100,000 person-years) and lung (RR=1.32, AR=22 per 100,000 person-years) cancer in women and melanoma in both men (RR=1.11; 95% CI 1.05-1.18) and women (RR=1.20; 95% CI 1.15-1.25). They also showed that patients with medical history of NMSC were more likely to be older and tended to burn and have more severe sunburns.

In population-based case-control study on NMSC (U.S.A) (5) (3584 participants: 1543 individuals with BCC, 1170 with SCC, 1416 age- and sex-matched controls) a significantly increased cancer risk after BCC was identified, that could not be explained by a variety of environmental, nutritional or behavioral risk factors, or by family history of cancer (adjusted HR=1.4, 95% CI 1.15, 1.71). In the site-specific analysis, BCC was associated with an increased risk of subsequent breast cancer (adjusted HR=1.13, 95% CI 0.62, 2.06).

A population-based cohort study (21) (Denmark; it included 37,674 patients followed for a maximum of 14 years after a first diagnosis of basal-cell carcinoma) showed that patients diagnosed with basal-
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cell carcinoma before 60 years of age (SIR=1.26) had a statistically higher risk for developing new cancer (P < 0.01) than did those diagnosed at 60 years of age or older (SIR=1.11). Also, the study revealed that patients with BCC had an increased risk of developing breast cancer, and that this risk was also significantly affected with age (SIR=1.37 in patients < 60 years of age compared with 1.05 in those > or = 60 years of age).

Another study (22) (Canada, 15,586 cases of BCC and SCC) reported a greater risk of female breast cancer following a BCC. Overall, the increased risk of developing a subsequent cancer was observed only in the first 4 years following a NMSC, although it remained increased for specific cancer sites and that the risk remained higher in all age groups up to 75 years of age. For breast cancer, the standard incidence ratios for developing the second primary cancer varied by time since diagnosis: SIR=1.47 for <1 year from BCC, SIR=1.26 for 1-4 years and SIR=1.22, for >5 years; the total SIR was 1.22 (95% CI 1.11-1.34).

**BCC after breast cancer**

Besides an elevated risk of contralateral breast cancer, women with a primary breast cancer are at increased risk of developing a subsequent non-breast cancer (attributed to genetic and other risk factors, and treatment: radiotherapy, chemotherapy and hormonal therapy).

Data concerning the incidence of BCC in breast cancer patients is scarce, due to mostly various registrations (regarding NMSC some registries include all types, others include only SCC, while others have no data on NMSC).

A cohort study (23) (13 population-based cancer registries in Europe, Canada, Australia and Singapore; included 525.527 women with primary breast cancer) identified an increased risk of NMSC (SIR=1.58). The variations on the time since first primary tumor and the age at breast cancer diagnosis are presented in table IV.

**TABLE IV**

SIRs for NMSC among 535,527 women with a first primary breast cancer by time since first primary breast cancer and by age at breast cancer diagnosis (23)

<table>
<thead>
<tr>
<th>Age at breast cancer diagnosis</th>
<th>Time since breast cancer diagnosis</th>
<th>SIR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1 year</td>
<td>1-9 years</td>
<td>1.23, 1.55</td>
<td>1.10-1.39</td>
</tr>
<tr>
<td>10+ years</td>
<td></td>
<td>1.77, 1.87</td>
<td>1.48-1.62</td>
</tr>
<tr>
<td>Pre-menopausal breast cancer  (45 years)</td>
<td></td>
<td>2.08, 1.87</td>
<td>1.55-2.31</td>
</tr>
<tr>
<td>Peri-menopausal breast cancer (46-55 years)</td>
<td></td>
<td>1.68, 1.55</td>
<td>1.45-1.82</td>
</tr>
<tr>
<td>Post-menopausal breast cancer (561 years)</td>
<td></td>
<td>1.51, 1.55</td>
<td>1.45-1.57</td>
</tr>
</tbody>
</table>

Recent studies focus more on the incidence of melanoma developing after a breast cancer diagnosis (SIRs ranging from 1.16 to 2.74) (24, 25, 26) and this risk was attributed especially to external radiation therapy (even at non-irradiated sites) (27).

In 2 cases of our 5 patients, which were diagnosed with BCC after breast cancer, the lesions were localized on the face (sun-exposed regions) and patients underwent radiotherapy as part of breast cancer management before the diagnosis of BCC.

Future knowledge about the impact of
risk factors and effects of treatment in breast cancer may add further explanations on the association of BCC, in addition to potential influences from increased surveillance and general cancer susceptibility.

CONCLUSIONS

In our study regarding breast cancer patients, 5 associated BCC. Unfortunately, extensive data on the incidence of BCC is unavailable in Romania. Due to their high frequency and low mortality, BCCs offer an excellent opportunity to study factors that put some individuals at increased risk of multiple malignancies. Thus understanding the shared risk factors that contribute to multiple malignancies may lead to new etiologic insights.

Also, knowing the risk of developing new primary cancers after breast cancer is important not only in relation to potential side effects of their cancer treatment, but also in relation to the possibility of shared etiology with other types of cancer.

CONSENT. This study was approved by the Ethics Committee of “Grigore T. Popa” University of Medicine and Pharmacy Iasi, Romania, and written informed consent was obtained from the patients for the research and publication of this study and any accompanying images.

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