HER2-Positive Male Breast Cancer with Thyroid Cancer: an Institutional Report and Review of Literature

Pooja Bardhan, Marilyn M. Bui, Susan Minton, Loretta Loftus, W. Bradford Carter, Christine Laronga, and Roohi Ismail-Khan

Department of Women’s Oncology, Comprehensive Breast Program, H. Lee Moffitt Cancer Center and Research Institute, Tampa, Florida

Abstract. We report a rare finding of two male breast cancer patients with HER2-positive breast cancer who also developed thyroid cancer. We reviewed 45 male breast cancer patients treated in our institution from 2003 to 2008. Only five male breast cancer patients were HER2-positive. In reviewing the published data, we found no cases of thyroid cancer and concurrent breast cancer in men. However, breast cancer and thyroid cancer have shown close association in women. This finding therefore provokes speculation as to whether we should investigate whether women with HER2-positive breast cancer are at a higher risk for thyroid cancer. Although this observation seems to be clinically prevalent, publications are sparse in clinical research areas linking thyroid cancer to breast cancer.

Key words: HER2 positive breast cancer, Thyroid cancer, Endocrine therapy, Trastuzumab, Integrated treatment and Invasive breast cancer

Introduction

In our institution, we noted 45 cases of male breast cancer from 2003 to 2008, of which only five patients were HER2-positive by fluorescence in situ hybridization (FISH) testing. We report on a rare finding of two of these male breast cancer patients with HER2-positive breast cancer who also developed thyroid cancer. Interestingly, in the HER2-negative male breast population, there were no occurrences of thyroid cancer. The following two cases were evaluated and reported in compliance with the University of South Florida’s Institutional Review Board Policy #311.

Case Study # 1

The first patient was a 68-year-old Caucasian gentleman with a history of diabetes, hypertension, and obesity. He presented to our institution with a large mass in the left breast. Physical examination revealed a 6-cm palpable mass with several palpable lymph nodes in the left axilla. Core biopsy revealed invasive ductal carcinoma, grade 3. His tumor was estrogen receptor positive at 80%, progesterone receptor positive at 70%, and HER2 overamplified (HER2/CEP17 ratio 2.4) by fluorescence in situ hybridization (FISH), as shown in Figure 1 (×600 amplification). Left axillary lymph node involvement was also demonstrated by fine needle aspiration, and pathological examination showed metastatic adenocarcinoma. Initial staging with computed tomography scans revealed a non-specific prominent calcified right lobe of the thyroid gland. A focused ultrasound of the thyroid revealed a solitary solid nodule with internal calcifications occupying the mid- and inferior portions of the right thyroid lobe, suspicious for malignancy. Ultrasound-guided fine needle aspiration of the thyroid nodule confirmed papillary thyroid carcinoma. Final staging for breast cancer was stage III (T3 N1 M0). The patient was treated with neoadjuvant chemotherapy and received 5 of 6 planned cycles of docetaxel and carboplatin with concomitant trastuzumab. He did not receive the sixth cycle because of possible capillary leak syndrome.

Address correspondence to Roohi Ismail-Khan; Division of Breast Oncology & Experimental Therapeutics; H. Lee Moffitt Cancer Center and Research Institute; 12902 Magnolia Drive, Tampa, FL 33612 (MCC-BR PROG); tel: 813-745-4933; fax: 813-745-7287; e-mail: Roohi.Ismail-Khan@moffitt.org
Cardiac evaluation was negative for findings of congestive heart failure, and trastuzumab alone was continued. After neoadjuvant chemotherapy, the patient underwent left mastectomy and complete axillary node dissection. Pathological examination revealed residual 1.5-cm invasive ductal carcinoma, grade 3, with a background of extensive fibrosis. There were 17 lymph nodes free of malignancy. The patient demonstrated a very good response to neoadjuvant trastuzumab-based therapy. Postoperatively, he had poor wound healing, which required debridement of the mastectomy skin flaps. He completed radiation therapy to the chest wall, and trastuzumab therapy was continued for a total of 18 treatments. Adjuvant endocrine therapy was started with Tamoxifen after completion of Herceptin. Five months later, he underwent right thyroid lobectomy. Pathology revealed multifocal papillary carcinoma with minimal extrathyroidal extension. Two separate carcinomas were present: one in the mid lobe – a papillary thyroid carcinoma measuring 1.5 cm x 1.3 cm x 0.8 cm; one in the superior lobe – a papillary thyroid carcinoma with follicular variant measuring 0.3 cm x 0.2 cm. The tumor at the mid lobe focally approached the anterior resection margin at less than 0.1 mm and was close to the posterior margin at 0.5 mm. The stage of the patient's cancer was stage III (T3 NX M0). Currently, he is being treated with thyroid suppression with Levothyroxine for his thyroid cancer and tamoxifen for his breast cancer. Patient did not have any family history of breast, ovarian, thyroid or colon cancer. He did have family history of prostate cancer.

Case Study # 2

The second patient, a 63-year-old Caucasian gentleman, presented with a mass in the right breast at an outside facility in September 2006. Ultrasound of the breast revealed a 3.5-cm mass and 4 to 5 enlarged axillary lymph nodes measuring 8-12 mm. An ultrasound-guided core needle biopsy confirmed invasive ductal carcinoma, grade 2. Core biopsy of the right axillary node also showed disease consistent with primary breast cancer. Complete staging workup showed no evidence of metastatic disease. The patient had a right modified radical mastectomy with a complete axillary lymph node dissection. Pathological examination revealed a 2.5-cm, high-grade, invasive ductal carcinoma with several additional satellite nodules in the breast tissue measuring between 2 and 10 mm. There was dermis and subcutaneous tissue as well as dermalymphatic involvement. The tumor was 2 mm from the deep margin. The tumor was estrogen receptor positive at 100%, progesterone receptor positive at 70%, and HER2 overamplified by FISH (HER2/CEP17 ratio 2.5). Of 16 lymph nodes, 5 were positive, with the largest node measuring 1.8 cm with extracapsular extension present. The patient began treatment with adjuvant chemotherapy. He had 4 cycles of doxorubicin and cyclophosphamide followed by 4 cycles of paclitaxel with trastuzumab. He was then started on tamoxifen and continued on to weekly trastuzumab. After completion of chemotherapy he was treated with radiation therapy to the chest wall and regional

Figure 1. Fluorescent in situ hybridization (FISH) image of amplified HER2 (X600 magnification). The breast cancer cell nuclei are stained with DABI counter stain. The orange-red signals represent HER2 gene; green signal for chromosome 17 centromere (CEP 17) control. HER2/CEP17 ratio is 2.4 indicates amplification of HER2 (cut off at 2.2).
nodes for 5 weeks. Five months after completing adjuvant chemotherapy, a follow-up PET scan showed uptake in the thyroid area. An ultrasound demonstrated a left thyroid mass measuring approximately 1.3 cm. The patient underwent a total thyroidectomy and a level 6 lymph node dissection was performed. He had a 1.3-cm papillary carcinoma (as shown in Figure 2) with 9 lymph nodes that were negative. Final staging revealed stage I thyroid cancer (T1 N0). He did not receive radioactive iodine ablation and was started on levothyroxine. Unfortunately, the patient had local recurrence eighteen months after diagnosis of breast cancer and four months after completing maintenance trastuzumab. He presented with nodules on the chest wall at the inferior aspect of the radiation field. These were biopsied and found to be consistent with recurrent breast cancer. He underwent local excision of chest wall mass and was then switched to anastrozole and leuprolide. The pathology was similar to the breast primary. He did well until early 2011, when he presented with disease progression to bone, liver, lung and chest wall. Hence he was switched to trastuzumab, lapatinib and zoledronic acid. Of note: patient had no family history of cancer. The clinical and pathologic characteristics of these two patients are summarized in Table 1.

Discussion

Breast cancer in men is rare, accounting for less than 1% of all breast cancers diagnosed yearly [1]. The incidence of breast cancer in men is steadily increasing [2,3]. In 2010, it is expected that there will be 1,970 new cases of male breast cancer diagnosed in the United States [2]. Male breast cancers are more likely than female breast cancers to express estrogen and progesterone receptors; over 90% are estrogen receptor positive [4]. In addition, men who have breast cancer are not likely to be HER2-positive. In one study, 61 slides of male breast cancer tissues from patients were assessed for HER2 overexpression. None of the samples showed amplification by FISH [5]. Because of the small number of men with breast cancer, it is impossible for single institutions to conduct randomized controlled studies on male breast cancers alone. Most of the information we have on male breast cancer is derived from retrospective studies and archived tissue banks, resulting in our treatment recommendations for men being based on these small retrospective studies or on data extrapolated from clinical trials conducted primarily with women [4]. It is well established that, after diagnosis of breast cancer, men are at a much higher risk than women of developing a second primary cancer [6,7]. In a retrospective study of 4,995 records from 1973 to 2004, 21% of men with breast cancer had other non-breast primary cancers and more non-breast primary breast tumors occurred after a diagnosis of breast cancer than before diagnosis of breast cancer [1]. Most of these were prostate, colon, and genito-urinary cancers [1]; notably, there were no thyroid cancers. BRCA2 mutations are the most common heritable factors in male breast cancer (15% of all patients), and carriers also have increased risk of prostate, pancreatic, and stomach
cancers as well as of melanomas [8]. Of note, BRCA1- and BRCA2-associated breast cancers are primarily HER2 negative.

Other familial syndromes do increase the risk for thyroid and breast cancer. Cowden syndrome is caused by mutations in the PTEN gene. It accounts for less than 1 percent of hereditary breast cancers. Male breast cancer has been reported in PTEN mutation carriers, but the specific risks are unknown [10]. Benign thyroid tumors (goiter and adenoma) are also common, and the risk for nonmedullary thyroid cancer, especially the follicular type, may be as high as 10% [11, 12]. Peutz-Jeghers syndrome (PJS) is an autosomal dominant condition caused by mutations in the STK11 gene. Carriers are predisposed to cancers of the stomach, colon, pancreas, small bowel, thyroid, breast, lung, and uterus.

Breast cancer and thyroid cancer have shown close association in women. Women with breast cancer have an increased risk of developing thyroid cancer, specifically papillary and follicular thyroid carcinomas, versus that shown in women with other types of cancer [9]. In reviewing the published data, we found no cases of thyroid cancer with concurrent breast cancer in men, noting that HER2-positive male breast cancer is a very rare phenomenon in and of itself. In our cases the HER2 amplifications are at low levels (2.4 and 2.5 respectively). This indicates that the increased incidence of thyroid

**Table 1. Comparison of patients**

<table>
<thead>
<tr>
<th>Patient (#)</th>
<th>Age (yr)</th>
<th>Breast Carcinoma</th>
<th>Thyroid Carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>68</td>
<td>Invasive ductal carcinoma Grade 3/3 Size 1.5 cm Angiolymphatic invasion absent Lymph node 0/17 ER positive (80%) PR positive (70%) HER2 by FISH amplified (2.4) Pathologic stage pT1cNXi-Mx after chemotherapy</td>
<td>Multifocal Papillary carcinoma (1.5 cm and 0.3 cm) Stage III T3 NX M0.</td>
</tr>
<tr>
<td>2</td>
<td>63</td>
<td>Invasive ductal carcinoma Grade 3/3 Size 2.5 cm Angiolymphatic invasion present Lymph node 5/16 ER positive (100%) PR positive (70%) HER2 by FISH amplified (2.5) Pathologic stage pT4b, pN2a, pMx</td>
<td>Papillary carcinoma Tumor size 1.3 cm and microscopic foci Lymph node 0/9 Pathologic stage pT1, pN0</td>
</tr>
</tbody>
</table>

ER, estrogen receptor; PR, progesterone receptor.
cancer in male breast may be mere coincidence. Papillary thyroid cancer is an indolent disease. Vigorous physical and radiological examination during breast staging may aid in early detection of thyroid cancer. This prompts the question of whether we should investigate whether women with HER2-positive breast cancer are at higher risk for thyroid cancer. Although this observation seems to be clinically relevant, publications are few and far between in clinical research areas linking thyroid and breast cancer in women.

**Implications for Clinical Practice**

Clinicians are aware that male breast cancer is a rare presentation, and that HER2-positive male breast cancer is an even rarer phenomenon. This report suggests that clinicians who do come across these rare patients should consider thyroid screening. To truly delineate the prevalence of this phenomenon, a larger cohort analysis should be considered in the future.

**References**