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Review

A role for the androgen receptor in the treatment of male breast cancer

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ABSTRACT

Male breast cancer (BC) is relatively rare, making up less than 1% of all breast cancer cases in the United States. Treatment guidelines for male BC are derived from studies on the treatment of female BC, and are based molecular and clinical characteristics, such as hormone receptor positivity. For female estrogen receptor positive (ER+) breast cancers, the standard of care includes three classes of endocrine therapies: selective estrogen receptor modulators, aromatase inhibitors, and pure anti-estrogens. In contrast to female ER+ breast cancers, there is less known about the optimal treatment for male ER+ BC. Furthermore, in contrast to ER, less is known about the role of the androgen receptor (AR) in male and female BC. We report here the treatment of a 28-year-old man with metastatic AR+, ER+ breast cancer otherwise refractory to chemotherapy, who has had a durable clinical response to hormonal suppression with the combination of aromatase inhibition (Letrozole) in conjunction with a GnRH agonist (Leuprolide).

1. Case

A 24-year-old man presented to his primary care physician with bloody discharge from his right nipple in 2008 (Fig. 1). The patient attributed the bleeding to trauma while lifting weights, but workup including a needle biopsy of the lesion was reported as stage I invasive ductal carcinoma staining diffusely positive (>76%) for both the estrogen (ER+) and progesterone receptors (PR+), and negative for human epidermal growth factor receptor 2 (HER2). Androgen receptor (AR) status was not reported. Staging workup did not reveal evidence of advanced or metastatic disease. Family history of malignancies including breast cancer, prostate cancer, pancreatic cancer, and ovarian cancer was negative. The patient reports having been exposed to very high levels of radiation in his occu-

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pation in the United States Air Force, though confirmation of the exact dose or nature of his exposure was not possible.

Right-sided mastectomy and axillary lymph node dissection ensued, and pathology demonstrated a 1.5 cm tumor with negative margins, pathologically staged as T1cN0MX. He received four cycles of adjuvant doxorubicin and cyclophosphamide, and his physician at that time treated him with anastrozole, as maintenance therapy. After one year of anastrozole, the patient was switched to tamoxifen due to side effects from anastrozole.

After four years on endocrine therapy, the patient noted the onset and worsening of musculoskeletal pain. A technetium bone scan revealed increased tracer activity in the posteromedial right tenth rib and left frontotemporal calvarium, concerning for skeletal metastases. A follow up chest CT revealed new pulmonary lesions with mediastinal, hilar and axillary lymphadenopathy (Fig. 2A). Biopsy of an axillary lymph node confirmed that the patient had a metastatic recurrence of his breast cancer. Immunohistochemistry (IHC) again demonstrated strong ER/PR positivity (100% expression for both), as well as strong AR positivity (100% expression) (Fig. 3). IHC for AR was performed after the ER/PR testing, based on a request from the medical oncologist while considering other potential treatments for him. The patient was treated with four cycles of capecitabine; however, subsequent CT scans revealed disease progression with increased size of the pulmonary lesions as well as the lymphadenopathy (Fig. 2B). The patient was then started on eribulin; after only two cycles, he developed a large malignant pleural effusion (Fig. 2C) and clinical deterioration necessitated hospital admission. Based on the demonstration of both ER and AR positivity from the lymph node biopsy, he was started on the combination of letrozole and leuprolide, with the goal of simultaneously blocking ER and AR receptor signaling, respectively.

Within 1 month following the initiation of combination ER and AR targeted therapies, the patient's pleural effusions resolved, and he experienced significant clinical improvement. Surveillance CT imaging revealed partial responses per RECIST criteria in all pulmonary lesions, axillary and retroperitoneal lymphadenopathy, and stable sclerotic bone lesions (Fig. 2D) that have now been maintained for over 28 months based on most recently available imaging. Clinically, he remains without any further evidence of disease progression.

2. Discussion

2.1. Epidemiology and genetics of male breast cancer

Male BC is a rare malignancy representing 0.5–1.0% of all breast cancers in the United States (Siegel et al., 2014). There were approximately 2360 new cases of male BC in the United States in 2014 and 430 estimated deaths due to the disease (Siegel et al., 2014). Male and female BC share similar risk factors, including advancing age and family history, as well as the BRCA2 mutation, which is the strongest known gene associated with male BC (Thompson and Easton, 2001). In addition to BRCA2, mutations in genes encoding for *AR*, cytochrome P45017 (*CYP17*), *PTEN* tumor suppressor, and *CHEK2* have also been implicated in the etiology of male BC (Weiss et al., 2005). Men with the XXY karyotype (Klinefelter syndrome) are at a 20–50 fold increased risk of developing breast cancer (Hultborn et al., 1996; Scheike et al., 1984) (Table 1). This increased risk is likely due to high levels of estrogens compared to androgens, as a result of increased levels of gonadotropins and low levels of androsterone. The vast majority of male BC (>90%) are invasive ductal carcinomas. Most male BC demonstrate ER and PR positivity—among patients with known receptor status from a series of 2500 patients with male BC, ER and PR positivity were 90.6% and 81.2%, respectively (Giordano et al., 2004).

Table 1
Risk factors in male and female breast cancer.

Risk factor	Male breast cancer	Female breast cancer
Higher age	X	X
Family history	X	X
BRCA1 or BRCA2 mutation	X	X
p53 mutations	X	X
History of therapeutic radiation	X	X
AR mutations	X	
Cytochrome P45017	X	
Loss of PTEN	X	
CHEK2 gene mutations	X	
XXY karyotype (Klinefelter's)	X	
Early menarche (<10)		X
Older age at first pregnancy		X
Nulliparous		X
Older age at menopause (>55)		X
Absence of breastfeeding		X

2.2. Initial management of male breast cancer

There are few data on the treatment of male BC based on randomized controlled trials due to the rare nature of this disease. Most treatment guidelines are extrapolated from the management of female BC; thus, treatment of male BC often mirrors that of female BC despite some notable differences. In early stage disease, most men receive a modified radical mastectomy rather than a lumpectomy (Golshan et al., 2007). This is primarily due to a paucity of breast tissue in men as well as the fact that male BC usually occurs in central locations. However, the role of breast conservation in men is expanding—in a SEER analysis of men treated between 1988 and 2003, 19% of men were treated with lumpectomy (Gnerlich et al., 2011). Furthermore, although men with early stage disease typically undergo axillary lymph node dissection, the use of sentinel lymph node biopsies is increasing (Albo et al., 2003).

2.3. Adjuvant therapy for male breast cancer

Given the established benefit of adjuvant chemotherapy in women at increased risk of recurrence based on a 21-gene recurrence score (21-gene RS) testing (Oncotype DX®), most clinicians will offer either an anthracycline or taxane-based combination to men who are deemed at a high risk of recurrence based on the presence of axillary lymph nodal disease, larger tumors, younger age, ER negative tumors (Early Breast Cancer Trialists' Collaborative Group, 2015; Paik et al., 2004). While the use of 21-gene RS has not been validated in male BC, Shak and colleagues found that male BC has a similar gene expression profile compared with female BC, as measured by the standardized 21-gene RS breast cancer assay (Shak et al., 2009). The use of 21-gene RS in a series of 65 male BC patients found a similar distribution of recurrence scores amongst men compared with women from the same time period, further corroborating that this testing may also be reasonable to help guide the treatment of early stage ER+, lymph node negative male BC (Grenader et al., 2014). However, further research is needed in determining the clinical efficacy of 21-gene RS in men.

For women with ER+ breast cancers, the standard of care for adjuvant therapy in early stage ER+ breast cancer includes endocrine therapy e.g. selective estrogen receptor modulators (SERMs); aromatase inhibitors (AIs); and pure anti-estrogens. Depending upon the tissue, SERMs (e.g. tamoxifen) can have agonist or antagonist effects on ER signaling. In breast cancer cells, SERMs exert antagonist effects, blocking ER signaling, which in turn leads to tumor cell death. Aromatase inhibitors (e.g. letro-

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