Case Report: Male Breast Cancer

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Abstract

Michael Dixon, one of the Program Directors of the 33rd Miami Breast Cancer Conference, presented a real case of male breast cancer, highlighting some of the issues surrounding its management and this is discussed here in this article. A 43-year-old man presented in 2002 with a painless breast lump. He had a strong family history, with his mother being diagnosed at age 50 and maternal aunt in her 40s. On examination, there was an 18mm lump just above the left nipple with numerous palpable small firm axillary lymph nodes. As part of the triple assessment, mammography and ultrasound of the breast and axilla was performed, which showed a 20mm suspicious mass in the breast and 4 abnormal nodes. Core biopsy revealed grade 2 invasive cancer of no special type, ER 8/8 (100% cells staining positively), HER2 negative. FNA of the axilla confirmed malignant cells.

Key words: male breast cancer, BRCA1, BRCA2, carrier mutation, tamoxifen, exemestane

Introduction

Male breast cancer (MBC) accounts for less than 1% of all breast cancers.[1] The average age of diagnosis of breast cancer in men is between 60 and 70 years, which is about 10 years later than that in women. The time from onset of symptoms to diagnosis in men is longer than in women (approximately 22 months) and as a result men often present with later stage disease, most likely due to a lack of awareness that men can develop breast cancer.[2]

Hormonal imbalance with excessive estrogen stimulation is associated with the etiology of MBC, which occurs in men with undescended testes, congenital inguinal hernia, orchiectomy, orchitis, testicular injury, infertility and Klinefelter's syndrome.[3] Klinefelter's syndrome, which is characterised by the 47XXY karyotype, small testes and gynecomastia, is associated with a 50-fold elevated risk.[4,5] Obesity and cirrhosis, which induce a hyper-estrogenic state, have also been implicated. As in women, radiation exposure is a risk factor for the development of breast cancer in men.[3] However, the majority of men with breast cancer have no identifiable risk factors, although between 15% to 20% of MBCs have a family history of disease.[6] MBC with multiple first-degree relatives with breast cancer suggest there may be a mutation in BRCA1 and BRCA2. Whilst male BRCA1 mutation carriers have approximately a 1.2% risk of developing breast cancer, male BRCA2 mutation carriers have a 6.3% lifetime absolute risk of breast cancer; this represents a 100-fold higher risk than that in the general male population.[7-9] Because of this, all men diagnosed with breast cancer should be considered for genetic counselling and BRCA testing, particularly those with young age at onset and a known family history of breast or ovarian cancer.

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Case

A 43-year-old man presented in 2002 with a painless breast lump. He had a strong family history, with his mother being diagnosed at age 50 and maternal aunt in her 40s. On examination, there was an 18mm lump just above the left nipple with numerous palpable small firm axillary lymph nodes. As part of the triple assessment, mammography and ultrasound of the breast and axilla was performed, which showed a 20mm suspicious mass in the breast and 4 abnormal nodes. Core biopsy revealed grade 2 invasive cancer of no special type, ER 8/8 (100% cells staining positively), HER2 negative. Fine needle aspiration (FNA) of the axilla confirmed malignant cells.

Genetic referral was discussed with the patient. He declined referral and consideration of genetic testing on multiple occasions. The young age at onset and significant family history indicate that there is a high probability that he has a genetic mutation, most likely BRCA2.

Pathology

The pathology of MBC is similar to that of female breast cancer. Ninety percent of MBCs are invasive; of these, 80% are of no special type (so called ductal), 5% are papillary, and 1% are lobular.[10] Lobular cancers are rare because of the lack of terminal lobular

duct units in male mammary tissue. Paget's disease of the breast and inflammatory breast cancers are as frequent in men as they are in women.[11] Ten percent of MBCs are non-invasive; almost all are DCIS, and most are of the papillary subtype and of low or intermediate grade.[12,13]

Men with breast cancer have a higher rate of hormone receptor positivity than women. A 25-year review of the Surveillance Epidemiology and End Results (SEER) database, which included 2357 MBCs, demonstrated estrogen and progesterone positivity in 90% and 80% respectively in males, and in 76% and 67% respectively in women with breast cancers.[11] Data on HER2 status is limited and inconclusive in male breast cancers. The rate of lymph node involvement and the hematogenous pattern of spread are similar to those found in female breast cancer.

FIGURE 1. Trapezius Muscle Wasting Due to Damage to the Accessory Nerve on the Left Side

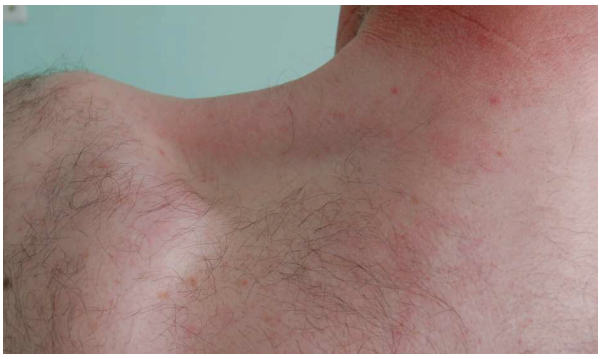
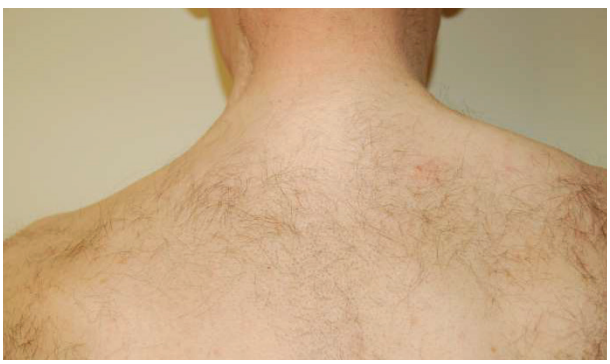


FIGURE 2. Good Outcome After Surgery



Surgical Management

The patient underwent left mastectomy and axillary lymph node dissection (clearance). Final pathology showed a 22mm invasive Grade 2 cancer, with margins greater than 5mm, extensive lymphatic-vascular invasion, and 16/28 involved nodes.

Simple mastectomy is the treatment of choice for the majority of MBCs, owing to the fact that there is minimal amount of mammary tissue in men and tumours are usually centrally located, although breast conserving surgery can be performed.[14] In a review of the SEER data, 1541 cases of MBC were identified, and almost 20% were treated with breast conservation.[15] For men who opt to proceed with breast-conserving surgery, adjuvant radiotherapy is essential following surgery. Locally advanced disease should be treated with neoadjuvant therapy followed by mastectomy. Axillary staging and management is the same as that for women. Sensitivity and specificity of sentinel lymph node biopsy in women and men are similar.[16,17]

The same guidelines used to make recommendations for adjuvant therapy in women with breast cancer should be used in men. Data have confirmed the benefits of adjuvant chemotherapy and hormonal therapy in MBC.[18,19] Although no trials have been conducted to determine indications for post-mastectomy radiation for MBC, it has been reported to reduce rates of local-regional recurrence, and guidelines for women are usually applied to men.[20]

The patient subsequently received a "Bonnadonna" regimen of chemotherapy, popular at that time, which involved 4 cycles of epirubicin and 8 cycles of CMF (cyclophosphamide plus methotrexate plus fluorouracil), and he received adjuvant radiotherapy to the chest wall and medial supraclavicular fossa.

Endocrine Management

This patient began taking tamoxifen 20mg per day. Response to hormone therapy correlates with presence of receptors, and is recommended in all men with estrogen receptor-positive cancers. Tamoxifen use, however, is associated with a high rate of treatment-limiting symptoms, such as hot flashes and impotence.[21] Endocrine therapy is the mainstay of treatment for hormone receptor-positive metastatic MBC. Tamoxifen is the drug of choice and, as in women, appears to improve overall survival.

Aromatase inhibitors in men are not well studied. In men, the testes produce 20% and the other peripheral tissues produce 80% of circulating estrogens. Aromatase inhibitors pose two potential problems in MBC, mitigating their efficacy. First, they may only partially block estrogen production, perhaps due to higher circulating androgen levels in men. Secondly, decreased levels of circulating estrogens induce the hypothalamus to produce more luteinizing hormone (LH) and follicle-stimulating hormone (FSH) that stimulate testicular hormone production, which can in turn increase estradiol (E2) production and circumvent inhibition of the aromatase enzyme. This may, in part, account for therapeutic resistance in aromatase inhibitors,[22] and so is often recommended that in men it is given in conjunction with a luteinizing hormone-releasing hormone (LHRH) analogue, such as goserelin, for androgen suppression.

Follow up consisted of annual clinical examination. The role for mammography of the contralateral breast is not known in MBC. In 2007, 5 years after diagnosis, the patient presented with an enlarged cervical node in the left posterior triangle, whilst still on tamoxifen. CT and MRI showed no other disease beyond this node and the node was considered to lie beyond the radiotherapy field. This was excised by a breast surgeon and showed an

involved node, with pathology similar to the initial diagnosis. Radiotherapy was considered but as there was no other disease evident, this was not given. The patient was switched to the aromatase inhibitor letrozole, and estradiol levels were checked after 6 weeks of treatment. These were undetectable and remained so at later checks. This indicated that letrozole was effective at blocking oestrogen production and there was no need to give an LHRH agonist in this man.

Case Progression and Complications

The patient presented 4 months after neck node excision with pain and stiffness in his left shoulder, with asymmetry of the posterior triangle of the neck. [**Figure 1**]. There was clear wasting of the trapezius muscle on the left side, which was considered to have occurred due to damage to the accessory nerve during the node biopsy. Studies have shown that damage to the accessory nerve occurs in 3% to 10% of node excisions in the posterior triangle of the neck.[23] Spontaneous recovery is infrequent. Early intervention can result in favourable outcomes, with 1 study reporting 107 out of 127 patients (87%) with improved functionality after repair, and greater than 95% improvement in the 29 patients where the nerve was found in continuity in those who underwent neurolysis.[23] This patient was referred to a specialist ENT surgeon for neck exploration. The nerve was found to be intact but was found in dense scar tissue and was released satisfactorily. He also underwent physiotherapy post-operatively with early and long-term improvement and good function ongoing [**Figure 2**].

In 2009, 7 years after diagnosis and 2 years after neck node excision, the patient presented with multiple further left small cervical metastatic nodes localised to the same area as before. There was no other disease found on CT or bone scan. He proceeded to have left selective node dissection, and pathology specimen showed 7/32 involved nodes grade 2 ER 100% positive.

Systemic therapy thereafter was a switch to exemestane 25mg. However, 2 years later in 2011 (9 years post diagnosis), further nodules were apparent and these were very slowly progressing during his exemestane treatment, with no metastases elsewhere. Two nodules measuring 6 and 7mm in size were locally excised in 2012, and the metastatic cancer in these nodes were ER 100% positive (Allred 8/8). This patient was managed by a switch back to tamoxifen. In 2013, 11 years after diagnosis and 6 years after the first node excision, further nodules appeared, but these have remained static on close monitoring and in 2016 are stable. He continues on tamoxifen, the activity of which is not as dependent on androgen or estrogen levels, with no symptoms and an excellent quality of life.

Conclusion

Overall prognosis is the same for men and women.[24] The impression that MBC has a worse prognosis may stem from the tendency toward diagnosis at a later stage. The same factors predict outcome in men and women: node status, tumour size and grade, and hormone receptor status. Axillary lymph node status is the most important prognostic factor. In a study of 335 cases of male breast cancer, node-negative patients had a 5-year survival rate of 90%, whereas node-positive patients had a rate of 65%.[25] Patients with estrogen receptor and progesterone receptor positive tumours had significantly improved survival compared to those with receptor negative tumours.[26]

In 2016, 14 years after diagnosis, the patient has stable disease and has been taking tamoxifen for 4 years. He still has a palpable small neck node but has no symptoms from it, is tolerating tamoxifen, and there has been no increase in size over the past year. This patient continues to decline referral to the genetics service.

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