Male breast cancer – neglected tumour

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Epidemiology

Malignant tumours of the male breast are rare. In the United States in 2010, about 1970 new cases of male breast cancer (MBC) were expected to be diagnosed, while in the same year 207,090 new cases of female breast cancer were expected [1]. The incidence of MBC is estimated at 1.1 per 100,000 a year [2]. Male breast cancer accounts for less than 1% of all malignant tumours in men [3]. Compared with female breast cancer, MBC occurs later in life and resembles postmenopausal breast cancer [2]. The median age of diagnosis is around 65 years. In contrast to female breast cancer, which occurs more frequently in white than in black women, there seems to be no racial imbalance in MBC. The incidence rate for MBC peaked in 1999 and seems to be declining in recent years. The incidence of MBC increases steadily with age. For female breast cancer there is a pause in the age-at-onset curve at around 50 years (Clemmesen's hook), which is absent in MBC. The risk of breast cancer death has decreased over the last 30 years, but less so in MBC.

Risk factors

Most of the known risk factors can be classified into one of two groups, genetic factors and hormonal imbalance.

It is estimated that about 20% of men with breast cancer report a family history of breast or ovarian cancer [4]. The strongest known risk factor for MBC is the presence of a germline mutation in the *BRCA2* gene [5]. Men carrying a *BRCA2* mutation have a lifetime risk of MBC of approximately 7%, 100 times higher than that of the general male population and similar to that of women with no family history of breast cancer. The association of MBC is stronger with *BRCA2* than with *BRCA1* mutations. Mutations in *CHEK2* (1100delC) also seem to increase the risk of MBC.

An altered ratio of oestrogen to testosterone in men seems to be an important risk factor for breast cancer. Patients with Klinefelter's syndrome (XXY karyotype) have low testosterone levels because of testicular dysgenesis, increased gonadotropins, and gynaecomastia. These patients have a lifetime risk of MBC of about 5% [4]. The correlation between gynaecomastia and MBC may point to an underlying risk factor for both conditions. Testicular conditions such as maldescensus, congenital inguinal hernia, orchitis and orchidectomy are associated with decreased testosterone levels and increase the risk of MBC. Also, the correlation between working in high-temperature environments and MBC might be mediated by testicular failure. Similarly, an increase in oestrogens, e.g. caused by alcoholic liver cirrhosis, obesity, or exogenous oestrogens used for treating prostate cancer, increase the risk of MBC.

Another known risk factor for MBC is radiation exposure with an estimated seven-fold risk increase per sievert of radiation exposure [6].

Biology

Male breast cancer shares many similarities with postmenopausal breast cancer in women. Most cancers are low-grade and hormone receptor-positive [7]. Most cancers are invasive ductal adenocarcinomas; however, a number of other subtypes (e.g. lobular, medullary, tubular, mucinous and squamous) have been reported in MBC [8]. HER2 over-expression has been reported in 16% of cases. Data on the proportion of androgen receptor-positive MBC vary widely, and the impact of androgen receptor expression on clinical course and treatment of MBC is unclear. Ductal carcinoma is situ (DCIS) is infrequently diagnosed in men (less than 10% of all MBC).

Screening

Men at increased risk of MBC (e.g. *BRCA2* mutation-positive, strong family history, Klinefelter's syndrome, prior personal history of MBC) should be advised to

carry out a monthly self-examination, undergo semi-annual clinical breast examination, undergo base-line mammography followed by annual mammography, if gynaecomastia and/or breast density is seen on baseline and to consider genetic counselling and testing [5].

Clinical presentation and diagnosis

Most patients present with a non-tender hard mass, frequently with nipple involvement and skin ulceration. MBC is usually diagnosed at more advanced stages than female breast cancer. The mean tumour size at diagnosis is 24 mm, slightly larger than in women and lymph node involvement is more frequent in MBC [2]. This is probably due to a lower level of awareness of breast cancer in men compared with women. The stage-specific survival rates when adjusted for sex-specific life expectancy and age at diagnosis show a similar prognosis for men compared with women with breast cancer.

Diagnosis is usually made by mammography, ultrasound and fine needle aspiration cytology [9].

Treatment of early MBC

The typical surgical treatment for early MBC is a simple or modified radical mastectomy with surgical assessment of the axilla. In clinically node-negative disease a sentinel lymph node biopsy followed by axillary clearance in cases with affected sentinel node seems adequate.

The indications for postoperative radiotherapy are less well-defined in MBC than in female breast cancer. However, it has been suggested that the recommendations used in female breast cancer should be followed [10]. Since breast-conserving treatment is rarely used in MBC, indications for radiotherapy are mainly axillary nodal involvement, large tumour size, skin involvement, and muscle invasion.

Adjuvant systemic anti-hormonal therapy is usually advised for hormone receptor-positive tumours, although no randomised studies have been reported to date. Usually tamoxifen is used at a dose of 20 mg daily for five years. A number of retrospective studies have suggested a clinical benefit of this approach. While aromatase inhibitors and GnRH agonists are occasionally used in adjuvant treatment, there are no data supporting this approach.

Adjuvant chemotherapy is sometimes used in younger patients, those with high-grade tumours and lymph node involvement in analogy to female breast cancer treatment recommendations. In a large series of non-metastatic MBC patients, adjuvant anti-hormonal treatment and chemotherapy both showed a benefit [11].

There are no data on the effect of adjuvant trastuzumab in HER2-positive MBC.

Treatment of metastatic MBC

Metastatic MBC is usually treated with endocrine agents. The preferred agent is tamoxifen, but aromatase inhibitors, GnRH agonists and the anti-oestrogen fulvestrant have all been reported to be active in individual patients [9]. Systemic chemotherapy is used in MBC in hormone receptor-negative cases or those resistant to endocrine therapy.

Conflict of interest statement

The author has no conflicting interests.

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