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Male Breast Cancer

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1. Synonyms

MBC

2. Definition

Male breast cancer (MBC).

3. Clinical Ffeatures

- **Incidence**: Breast cancer in men is rare and accounts for 1% of all breast cancer diagnoses. In the UK, some 350 men are diagnosed annually with around 2470 in the USA. Data from cancer registries in the UK and USA suggests that the numbers of men receiving a breast cancer diagnosis has been rising gradually since the 1970s.
- **Age**: Typically over 60, although all ages can be affected.
- **Sex**: Breast cancer is found predominantly in women, but it can also affect men. Breast cancer in men is around 100 times less common than it is in women.
- **Site**: Breast tissue in men is typically situated directly behind the nipple.
- **Clinical presentation**: A unilateral, firm, painless, or minimally tender mass behind or adjacent to nipple or in axilla; changes in appearance of the nipple, e.g., inversion; and nipple discharge or bleeding. Because MBC is perceived by the majority of general public as a gender-specific condition, men often postpone presenting to doctors with symptoms, which can result in delays in diagnosis. The diagnostic pathway for MBC is similar to that used in women where breast cancer is suspected. While screening mammography is not recommended, due to small amounts of breast tissue in men, paradoxically this makes palpation of a suspicious lesion easier. Diagnosis is based on physical examination and biopsy. Sentinel lymph node biopsy is also used to identify positive nodes ("Sentinel Node").

- **Treatment**: The absence of gender-specific trials for breast cancer means that men are treated in exactly the same way as women. Usually this mastectomy is followed by chemotherapy and radiotherapy. Some men opt for breast-conserving surgery, if appropriate, because of reduced morbidity and a better cosmetic outcome. As most MBCs express estrogen receptor, they are suitable for treatment with endocrine therapy, predominantly adjuvant tamoxifen. Data from clinical trials such as ATAC, in which the efficacies of aromatase inhibitors (AIs) were compared to tamoxifen, have revolutionizsed the treatment of breast cancer in post-menopausal women, such that AIs are now considered first-line therapy. Despite the fact that aromatase is expressed in MBC, initial case series have shown negative or equivocal results meaning the efficacy of aromatase inhibition in men has been questioned. Because of the increase in testosterone seen after aromatase inhibition, this may overcome the effect of AI blockade, by saturating the enzyme pathway with substrate, resulting in only a modest suppression of estrogen. Hence LHRH agonists are required to reduce excessive substrate and maximizse the effect of aromatase inhibition. As a result, AIs are generally contraindicated in MBC, unless used with medical or surgical orchiectomy.
- **Outcome**: About 80 men will die of breast cancer in the UK each year. In the USA, this is around 460. Survival rates for MBC are generally assumed to be lower than female breast cancer, probably as a result of presentation at a more advanced stage than in women. However, in general, studies in which male and female breast cancer are matched for key prognostic factors (size, grade, and lymph node status), have refuted this, with outcome almost identical between genders.

4. Macroscopy

Most specimens are mastectomies (Fig. 1a) with either sentinel node biopsy or axillary node clearance according to the pre-surgical nodal assessment results. The macroscopic tumours are often large, with frequent skin and nipple involvement (Fig. 1b). Similar to the female type, the tumour may appear circumscribed and, infiltrative or show cystic changes.

Fig. 1 (**a**) A mastectomy specimen with orientation sutures. It includes fibrofatty breast tissue with an overlying nipple bearing ellipse of the skin. The surgical margin is painted. (**b**) Slicing of the posterior surface shows a well-defined, graeyish-white haemorrhagic tumour. The tumour is clear of surgical margins

5. Microscopy

The main histological types and their frequency in MBC areis shown in Table 1. Of these, the commonest type of MBC is invasive ductal carcinoma of no special type (NST) -Invasive Carcinoma NST- of grade 2

differentiation (Fig. 2). The tumo~~u~~rs comprise nests and trabecula of malignant cells within fibrous stroma. Invasive lobular carcinoma is extremely rare and so is lobular carcinoma in situ. Compared with female breast cancer, incidence of papillary carcinoma (both intraductal and invasive) and mucinous carcinoma is higher in the male breast (Shaaban~~,~~ et al. 2012). Ductal carcinoma in situ (DCIS; "Ductal Carcinoma In Situ") is reported in 5–15% of cases. Reporting of MBC and cancer datasets is~~are~~ the same as for female breast cancer.

Fig. 2 (H&E) image of the most frequent type of MBC, ductal carcinoma NST

6. Immunophenotype

A meta-analysis of 1986 cases, designed to identify common features of MBC, showed that MBC is typically ERα- and PR-positive, with HER2 expression infrequent (Humphries~~,~~ et al. 2017). This is in line with preliminary results reported from the EORTC10085, TBCRC, BIG, and ~~the~~ NABCG International Male Breast Cancer Program and other smaller studies from single centers. This is illustrated in Table 2. As with female breast cancer, ERα and PR are used to guide treatment and prognosis in MBC ("Hormone Receptors in Breast Cancer"). Other biomarkers that have been examined in MBC using immunohistochemistry include~~:~~ AR, ERβ1, ERβ2, ERβ5, Bcl-2, p53, E-cadherin, Ki67, survivin (both in the nucleus and cytoplasm), prolactin, and FOXA1. While these biomarkers are not unique to MBC, some of them, e.g., AR, is frequently expressed at relativity high levels in men. Although AR is currently not used for routine diagnostics or management in MBC, its relative abundance suggests that this could be used as a therapeutic target for anti~~-~~androgen therapies. Examples of ERα, PR, and AR expression in MBC are shown in Fig. 3.

Fig. 3 Immunohistochemical examples of hormone receptors which are commonly expressed in MBC. ERα (**a**), PR (**b**), and AR (**c**) are frequently expressed

Although ERα expression is higher in MBC than in female breast cancer (typically in approximately 80% of MBCs vs. 60–70% of female breast cancers), it has been proposed that not all ERα-positive MBCs behave in the same way as their female counterparts. This is founded through observations of different grouping of hormone receptor patterns when applying hierarchical clustering. In female breast cancers, PR and ERα clustered together, while in MBC, ERα clustered together with ERβ and AR, with PR clustering independently (Shaaban~~,~~ et al.~~,~~ 2012). Further cluster analysis in MBC showed significant correlation of ERα, AR, and FOXA1 (Humphries~~,~~ et al.~~,~~ 2017).

A number of cell cycle proteins have also been examined in MBC. Enhanced proliferation seems to be associated with poorer outcome in MBC, exemplified analysis of proliferation by mitotic count, and the expression of cyclins -A, -B, and −D1 biomarkers.

7. Molecular Ffeatures

MBC is identical to female breast cancer histologically;, however data from molecular profiling studies using a variety of platforms is starting to suggest there may be underlying gender-specific biological differences in their genomic landscapes, both genetically and epigenetically.

As reported above, in general, the main histological subtype observed in MBC is ductal NST with the most common phenotype ER- and/or PR-positive;, HER2-negative, which falls into the luminal A-like subgroup, is used to stratify female breast cancer. However, one of the first gene profiling studies to compare male and female breast cancer showed two unique subgroups of MBC, termed luminal M1 and luminal M2 (Johansson, et al. 2012). These differed from the conventional molecular classifications observed in female breast cancer. Consequently, the same group reported differential driver genes in MBC vs. female breast cancer. Somatic genetic alterations typically seen in ERα-positive/HER2-negative female breast cancers (the most common phenotype seen in MBC), e.g., PIK3CA and TP53 mutations and 16q loss, were much less frequent in subtype-matched MBC, suggesting that MBC is driven by different somatic changes (Piscuoglio, et al. 2016). In a number of smaller studies, gender-specific differentially expressed genes, including those involved in translation, cell migration-/-motility, immune response, membrane transport, apoptosis, and energy metabolism, have been reported, adding weight to the hypothesis that male and female breast cancers are biologically distinct.

Promoter hypermethylation has been reported in MBC with methylation of a number of genes that are known to act as tumor suppressors. Accumulation of methylated genes and an overall high methylation pattern wereas correlated with a more aggressive phenotype and poorer survival. Interestingly, RASSF1A, a well--characterizsed tumor suppressor gene, was significantly more frequently methylated in MBC than female breast cancer, providing further evidence of likely biological differences between genders.

Expression of microRNAs (miRs), small noncoding RNAs that alter gene expression at the post-transcriptional level, has been examined in MBC. Differential expression of several miRNAs has been reported between gynaecomastia and MBC and also between MBC and female breast cancer. Despite these observational reports, the role of miRs in MBC, and if this may contrast from female breast cancer, has not been studied fully.

Germline mutations of BRCA2 and, to a lesser extent, BRCA1, are associated with increased risk of men developing breast cancer (approximately 5–10% and 1–5%, respectively). A genome-wide association

study of MBC identified a SNP in RAD51B which was associated with MBC susceptibility, but there is evidence that common variants associated with female breast cancer may also impact MBC risk (Orr~~,~~ et al. 2012). More recent genotyping of 1802 male carriers of BRCA1/2 mutations showed that weighted polygenic risk scores based on 88 female breast cancer susceptibility variants were similarly associated with breast cancer risk in men (Lecarpentier~~,~~ et al. 2017). A large ongoing study into the causes of MBC has identified several genetic variations associated with risk of developing the disease. These genetic variations appear to have a different effect on risk ~~in on risk~~ between genders, lending further support to the idea that the biology of breast cancer is diverse in men and women.

8. Differential D~~d~~iagnosis

The most important differentials are gynecomastia, a benign enlargement of the male breast ("Gynecomastia") and metastases to the breast, such as metastatic prostatic carcinoma, melanoma, ~~…~~etc. Gyn~~a~~ecomastia may present with florid hyperplasia of the mammary ducts which can mimic in situ carcinoma particularly on small biopsy or in cytological preparations. Attention to the architectural features of hyperplasia, admixture of luminal and basaloid cells, and the absence of significant atypia support a benign diagnosis. Basal cytokeratins such as CK5 and CK14 show a ~~3~~ three-~~-~~layered ductal epithelium in gyn~~a~~ecomastia (Kornegoor~~,~~ et al. 2012) and negative staining in DCIS. Metastases to the breast should be identified by clinical correlation, unusual histological features, and a suitable panel of immunohistochemical biomarkers.

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Table 1 Main histological subtypes observed in MBC and their relative frequencies

Histology	% Frequency
Ductal NST	85
Lobular	1–2
Papillary	3–5
Mucinous	1
Medullary	0.5
Cribriform	0.5–1
Tubular	0.5
Mixed	5

Data was obtained from several published articles, including the Veterans Affairs (VA) Central Cancer Registry and (Shaaban et al. 2012)~~.~~

Table 2 Overview of the clinicopathological features of MBC in ~~sixteen~~ 16 published studies examining a total of 1986 cases from 1996~~–~~ to 2017

Feature	Number (%)
Histology	
Ductal	1615 (84)

Lobular	19 (1)
Other	239 (12)
N/A	60 (3)
Grade	
1	239 (13)
2	872 (48)
3	597 (33)
N/A	115 (6)
Node	
+	734 (42)
−	742 (42)
N/A	275 (16)
ERα	
+	1584 (86)
−	193 (10)
N/A	74 (4)
PR	
+	1321 (72)
−	436 (24)
N/A	84 (5)
HER2	
+	160 (9)
−	1319 (77)
N/A	241 (14)

Data adapted from Humphries et al., 2017, where details on specific studies can be found.

N/A not available.