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Controversies in clinicopathological characteristics and treatment strategies of male breast cancer: A review of the literature

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ABSTRACT

Male breast cancer (MaBC) is a rare disease, accounting for less than 1% of malignancies in men. For this reason, literature data on its clinicopathological characteristics are very heterogeneous and treatment strategies have mostly been extrapolated from the female counterpart. However, immunohistochemical peculiarities of MaBC have recently emerged, defining it as a distinct entity from female breast cancer (FBC), thus requiring a tailored clinical approach. MaBC appears to be more often hormone receptor positive than FBC, while data on HER2 status still remain inconclusive, indicating a possible higher incidence of HER2 alterations.

Treatment strategies for MaBC have evolved and less invasive local treatments such as lumpectomy and sentinel lymph node biopsy have become part of everyday clinical practice, while there are still controversies on the indication of radiotherapy, especially after mastectomy. Similarly, differences between male and female hormonal status have raised some concerns in the use of aromatase inhibitors in male patients and the choice of best endocrine therapy is still controversial.

1. Introduction

Male breast cancer (MaBC) is a rare disease, accounting for less than 1% of breast cancers and less than 1% of malignancies in men (Siegel et al., 2012). Recently, rates for female breast cancer (FBC) incidence have shown a slight increase, especially among women

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above the age of 60 and between the age of 20 and 39 (DeSantis et al., 2016). Some authors indicate an increasing incidence trend also for MaBC, from about 1.0 per 100.000 in the late 1970s to approximately 1.2 per 100.000 at the start of this decade (Speirs and Shaaban, 2009). Due to his rarity, MaBC has not been thoroughly investigated in terms of its biological characteristics and treatment strategies. Indeed, male patients are only exceptionally accepted for entry in clinical trials of breast cancer and no prospective randomized trials have been designed exclusively for MaBC. Consequently, most of our understanding of MaBC has been extrapolated from knowledge of FBC. Although biological and endocrine features of MaBC have been reported in several published case series, the same prognostic and predictive markers are used to determine optimal management strategies for both men and women diagnosed with breast cancer. In this review, we discuss the clinicopathological similarities and differences between MaBC and FBC, and describe the current clinical approach in the local and systemic settings for MaBC.

2. Controversies in clinicopathological characteristics

2.1. Immunohistochemical and molecular definitions

What is known on the biological characteristics of MaBC derives from small, usually retrospective single institution studies, from which it is difficult to extrapolate a real trend in the expression of biological variables. In the next paragraphs we will discuss each of the most relevant in details, although we cannot deny that there is a unanimous agreement on the high expression of oestrogen and progesterone receptors (ER and PgR) and the prevalence of ductal histology.

In a meta-analysis published in 2006, the predominant histological type of MaBC was invasive ductal, accounting for more than 90% of all male breast tumours (Fentiman et al., 2006). This finding is consistent with more recent case series reports. Specifically, in Bradley et al. a comparison between MaBC and FBC showed that the most common histology was infiltrating ductal carcinoma, present in 154 (97%) men and 812 (86%) women with a statistically significant difference between genders (Bradley et al., 2014). A similar significant difference was reported also by Iorfida et al. (Iorfida et al., 2014) and Shaaban et al. (Shaaban et al., 2012). Ductal invasive carcinoma was reported in 94% and 83% of MaBC patients in the two studies, respectively, and a statistically significant difference was noted with the matched female series. Lobular histology is very rare in MaBC and this is probably due to the anatomical structure of male mammary gland. In fact, in contrast to the female breast which is predominantly comprised of ducts, glandular epithelium and non-adipose stroma, the male breast is mostly adipose tissue with sparse ducts and periductal stroma (Vandenberga et al., 2013). The anatomical and functional importance of ducts in female breast is highlighted by the lobes organization: the glandular tissue is composed of lobes that comprise lobules containing 10–100 alveoli drained by numerous small ductules of the ductal system (Hassiotou and Geddes, 2013). This more complex anatomy with both ductal and lobular system well represented, may explain the more heterogeneous histology of FBC.

Biomarkers such as Ki-67 labelling, HER2 overexpression and nuclear grading are analysed in addition to ER and PgR to describe the subtle biological differences and define different risk profiles between MaBC and FBC. In the last 15 years, a large research effort has been devoted to the analysis of gene expression patterns to determine molecular signatures associated with a more exact risk profile. Basically, proposing that a phenotypic diversity might be accompanied by a corresponding diversity in gene expression patterns that could be captured using cDNA microarrays, Perou et al., used a hierarchical clustering method and grouped genes on the basis of similarity in the pattern with which their expression varied over all samples (Perou et al., 2000). These microarray profiling studies based on the “intrinsic” gene set have identified five distinct subtypes in FBC (luminal A/B, HER2 enriched, basal and normal-like) that lately showed to be associated with significant differences in relapse-free survival (Reis-Filho and Pusztai, 2011). This molecular approach was an important step forward to a deeper understanding of breast cancer biology, but due to the costs and tissue handling requirements associated with transcriptional profiling, the most common approach is now to use surrogate assays based on immunohistochemistry (IHC). A partial approximation of the molecular classification can thereby be obtained by using the expression levels of a small number of proteins (ER, PgR, HER2, Ki-67, CDK5/6) that can be assessed on paraffin-embedded archival tumour material to generate surrogate IHC-based definitions for classifying breast cancers into the intrinsic subtypes. Many authors have used the intrinsic subtype definitions searching for substantial biological differences between male and female breast cancer. Ge analysed 42 MaBC cases, using IHC to assess ER, PgR and HER2 status, the latter confirmed, when found 2+ at the immunostaining, with fluorescence in situ hybridization. Then, the author grouped the patients into luminal A-like (ER+ and/or PgR+, HER2-), luminal B-like (ER+ and/or PgR+, HER2+), HER2 enriched-like (ER-, PR-, HER2+), and basal-like (ER-, PR-, HER2-, CK5/6+) tumours (Ge et al., 2009). The luminal A-like subtype was found to be the most common subtype (83%, 35/42), followed by the luminal B-like subtype (17%, 7/42), whereas the author did not identified any basal-like nor HER2 enriched-like subtypes (Ge et al., 2009). Speirs and colleagues, in a study matching 260 MaBCs to their analogue female counterpart, found that luminal A-like subgroup was the most common phenotype in both sexes, while luminal B-like was not seen in males and basal-like tumours were infrequent in both (Speirs and Ball, 2010). Yu et al. published a study of 68 cases of MaBC collected retrospectively to identify molecular subtypes: 41 cases (60%) were luminal A-like, 17 cases (25%) luminal B-like, 6 cases (9%) HER2 enriched-like and 4 cases (6%) basal-like, showing that patients with ER/PgR positive accounted for 85%, while the proportion of HER2 positive was 35% (Yu et al., 2013). Kornegoor et al. analysed 134 MaBC cases and observed that 75% were classified as luminal A-like, 21% as luminal B-like and the remaining 4% of cases as basal-like; no HER2-driven cases were identified (Kornegoor et al., 2012). Shaaban et al. published a matched series of MaBC and FBC with 251 and 263 cases, respectively: luminal A-like was seen in 98% of males and 90% of females, luminal B-like or HER2 subgroups were not observed in males but found in 6 and 2% of females, respectively, while basal-like tumours were infrequent in both cohorts (2% in each) (Shaaban et al., 2012). On overall, these studies show that the two genders are very similar in terms of immunohistochemical profile, but subtle differences can emerge when probed more deeply using the intrinsic subtypes classification.

2.2. Hormone receptor status

From the numerous case series that have been published we can infer that the vast majority of patients with MaBC population presents with an ER and PgR positive disease. In one of the largest comparative studies of male versus female breast cancer, data were collected from the National Cancer Institute’s Surveillance, Epidemiology, and End Results (SEER) Database from 1973 through 2005 (Anderson et al., 2010). From the analysis of around 34.000 FBC and 2.600 MaBC, 77.5% and 92.4% of breast cancers were ER positive in women and men, respectively. Discussing those data, the Authors outlined that the descriptive patterns show that the biology of MaBC resembles the late-onset and ER-positive type of FBC, referring to the bimodal characterization (early-onset