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MALE BREAST CANCER: SIGNS, SYMPTOMS, AND TREATMENT: A REVIEW

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Abstract: Male breast cancer (MBC) is an infrequent and uncommon condition. It accounts 1% than other cancer diagnosed in men. The rationale for low incidence among men is due to difference in hormonal environment and relatively poor breast tissue count in men. The disease is also diagnosed at later stages because of lack of awareness. In Asia most of the males hide about this disease due to social psychology. There is limited literature and published data on MBC due to low incidence of disease. This review deals with etiology, pathology, risk factors, treatment and psychological trauma in MBC patients. While in both genders breast carcinomas share similar features, significant variations exist. Most studies are very limited on the men with breast cancer. Therefore, most evidence on male breast cancer is extracted from female research. However, we will learn more about them when a lot of these little studies on male breast cancer are put together. This review stresses on the occurrence, etiology, clinical characteristics, diagnosis, treatment, pathology, survival and MBC-related prognostic factors.

Keywords – Male Breast Cancer, Female Breast Cancer, Disease

I. INTRODUCTION

Male breast cancer (MBC) is an unusual or atypical and rare disease. It accounts 1% than other cancer diagnosed in men. Most of the cases are reported in United States around 14,00 cases every year and as compared to women nearly 184,000 cases reported. The disease is assumed to be caused due to disorder linked with abnormal estrogen metabolism and absorption ⁽¹⁻³⁾. The explanation for low incidence between men is due to difference in hormonal environment and relatively poor breast tissue count in men. The disease is also diagnosed at later stages because of lack of awareness. In Asia most of the males hide about this disease due to social psychology. There is limited literature and published data on MBC due to low incidence of disease. This review deals with etiology, pathology, risk factors, treatment and psychological trauma in MBC patients.

The number of cancers diagnosed in men is less than 1% of breast cancer and the number of cancers diagnosed in men is about 1% ^(4,5). Male breast cancer meets the EU ⁽⁶⁾ and US ⁽⁷⁾ rare cancer classifications, classified as roughly 6 cases per 100,000 or 15 cases per 100,000 individuals, respectively. MBC is associated with substantial morbidity and mortality, most likely due to lack of knowledge in the general public, as men are typically more experienced and older while comorbidities can be confusing ⁽⁸⁾. The occurrence of MBC varies according to geographic position. In U.S.A. and U.K., it is higher than in Finland and Japan ⁽⁹⁾. Incidence rates of breast cancer in men increase gradually with age as they do in women, but the average age of initial breast cancer diagnosis is five years higher in men (67 years) than in women (62 years). Risk factors for male breast cancer include a family history of breast cancer, chest or breast radiation exposure, black origin, genetic mutation of the germline (e.g.,

BRCA2, BRCA1, CHEK2, PALB2), use of exogenous estrogen, and hyper-estrogen-related diseases (e.g., Klinefelter syndrome) ^(4,10).

The cancer incidence in men is more in North America and Europe, whereas the rate is low in Asia ⁽¹¹⁾. According to the American Cancer Society it is estimated that 1,450 men were estimated to cause breast cancer in the United States and there is a probability that they may die also due this disease and the number may vary to 470 in the upcoming years ⁽¹²⁾. Because of its rarity, the biological behavior of the disease is not well known, and there are no definite guidelines regarding the optimal therapeutic approach. The trend worldwide is to treat it in a fashion similar to female breast cancer. There is less published data found on male breast cancer in India. This inspired us to do a retrospective study on patients with male breast cancer. Unfortunately, both the primary health care system and the general public have given very little focus on male breast cancer. Both communities are unaware of the disease and are also unaware of its possible physical and psychological consequences ^(13, 14). The breast cancer varies in men and women both physically as well as psychosocially. Probably Because often the disease is perceived as “a woman’s disease,” Little research has been done on the point of views and demands of breast cancer sufferers ^(15 - 17). But like other disease, breast cancer was also reported in men during age group of 5 to 93 years ⁽¹⁸⁾.

As variation in age reported in different studies, similar way there are other factors also responsible for causing this disease which includes diet habits. The change of diet and use of Increasing levels of obesity due to physical inactivity and sedentary lifestyle are a serious public health problem in both the US and UK and may contribute the risk of causing male breast cancer ⁽¹⁹⁾. The symptoms also vary men, majority of cases reported painless subareola mass, other symptoms may include areola pigmentation, erythema or ulceration, gynaecomastia, and nipple discharge/retraction. The major treatment possibility in male and female is surgery of breast ⁽²⁰⁾. Due to social psychology, screening in men is less or negligible than female. MBC is diagnosed at a younger age and with a more serious clinical appearance than in women, with a larger tumour size and a more frequent presence in lymphonodal disease ⁽²¹⁾. Mutation is one of the variables in MBC, about 10 per cent of men with Male Breast Cancer have a BRCA2 mutation, and less have a BRCA1 mutation ⁽²²⁾. PTEN, p53, and CHEK2 are other genes confirmed to have mutated in male patients ⁽²³⁾. Unlike the extensive literature on female breast cancer, less attention has been paid to male breast cancer, particularly regarding prognostic factors and systemic therapy ⁽²⁴⁾. Most male breast cancer care algorithms are currently extrapolated from the treatment and data on post-cancer monitoring for male breast cancer survivors are especially lacking ⁽²⁵⁾.

II. RISK FACTORS

Male Breast Cancer is possibly to be triggered by the combined effects of multiple risk factors, including psychiatric conditions linked to hormonal changes, exposures to work and environment, and genetic risk factors, such as a strong history of breast cancer in the family and mutation attributable to predisposing genes, such as BRCA genes and probably environmental factors, particularly occupational carcinogenic exposure, may contribute to MBC risk through interaction with genetic factors. Several studies have documented a clear correlation in male hosts of BRCA1/2 gene mutation between a particular occupation and the risk of breast cancer ⁽²⁶⁾. The pathogenesis of MBC is uncertain, but hormonal stage may play a significant role in the disease’s progress. Testicular defects such as congenital inguinal hernia, infertility, orchitis, and undescended testicles were strongly

associated with risk elevations ⁽²⁷⁾. Researchers had reported gynecomastia has been known in men who have with breast cancer ⁽²⁸⁾. BRCA gene mutations are some of the most clearly known risk factors for men with breast cancer. BRCA1/2 genes are tumor suppressor genes are concerned with DNA repair, 5 to 10 percent of women with breast cancer have mutations in these genes ⁽²⁹⁾. There is scientific proof that by the age of 80 a man with BRCA2 gene mutation has a risk of disease's development of 7 percent, which is higher for men in the general population. It should be noted that having a mutation of the BRCA2 gene also implies a bigger risk for several cancers, including prostate and ovarian cancers ⁽³⁰⁾. Alleged risk factors for male breast cancer include conditions that may or may be associated with hormonal imbalances (such as obesity, liver disease, and Klinefelter syndrome), high consumption of alcohol, older age, and treatments that modify normal male hormones (such as prostate cancer treatment). Many possible risk factors include a prior record of testicular disorders (such as cryptorchidism or mump orchitis) or radiation exposure ⁽³¹⁾. For people exposed to high electromagnetic fields, an elevated incidence of MBC has been identified. Several studies have shown that a significant level of risk is also correlated with polycyclic aromatic hydrocarbons (PAHs) ⁽³²⁾. In male patients with breast cancer, mutations in the androgen receptor gene, PTEN (Cowden's syndrome), and mismatch repair genes (hMLH1) were established ⁽²⁾. One study indicated that decreased of AR activity in the breast could predispose MBC to grow earlier ⁽³³⁾. High estrogen receptor positivity in MBC could be due to decreased levels of estrogen leaving receptors accessible for binding, which is possibly necessary for successful hormonal response ⁽³⁴⁾. Obesity, liver disease, elevated plasma cholesterol, and the occurrence of gallstones are disorders associated with increased rates of endogenous estrogens that are often correlated with an increased risk for the MBC development ⁽³⁵⁾.

III. PATHOLOGY

Male breast cancer (MBC) tends to be clinically identical to female breast cancers, however there are few important variations in pathology. MBC is primarily ductal in nature because male breast usually contains no lobules and ducts only ⁽³⁶⁾. Since the breast tissue of men is elementary, it generally does not distinguish the difference and develop lobule unless revealed to elevated concentrations of endogenous or exogenous estrogen. Consequently, the prevalent histological type of infection is aggressive ductal, containing 90 percent or more than that of all male breast tumors ⁽³⁷⁾. In the Screening, Epidemiology and End Results (SEER) cancer study, figures from over 2000 masculine patients suggest that 93.7 percent of male breast cancers are ductal or unclassifiable, 2.6 percent are papillary, 1.8 percent are mucosa, and only 1.5 percent are lobular. Around 90 percent of male breast cancers shows the estrogen receptor, and 81 percent shows the progesterone receptor ⁽¹⁶⁾. It was observed by Bloom et al. that only one out of 58 male breast cancers overexpressed *her2-neu* and that none of 58 had gene amplification ⁽³⁸⁾. The histological identification of aggressive MBC is according to the guidelines of WHO, 2012. Histological subtypes vary in prevalence between women and men, with aggressive cancers of no specific forms being perhaps the most common subtype (>90%). This is accompanied by invasive papillary carcinoma and aggressive micro papillary carcinomas that are more commonly seen in men ^(39, 40).

IV. HOW DIFFERENT FROM FEMALE BREAST CANCER

Breast cancer in men is close to breast cancer in women, in several respects even though there are considerable variations ⁽⁴¹⁾. It seems that most of MBC management is based on the clinical knowledge acquired from the treatment of female patients with breast cancer. However, literature reports show some conflict as to if MBC has a similar prognosis and disease symptoms to female breast cancer ⁽⁴²⁾. MBC appears to develop at an advanced age, with even more severe lymph node metastases and an elevated proportion of estrogen receptor–positive (ER+) tumors related to female breast cancer ⁽⁴³⁾. Compared to female breast cancers, MBC shows oestrogen receptor (ER) and progesterone receptor (PR) (ER > 90 vs. 76 percent, PR > 75 vs. 60 percent in FBC) more commonly ⁽⁴⁰⁾. It seems that MBC is more common to develop inside the setting of a *BRCA2* gene mutation rather than *BRCA1* gene mutation ⁽⁴⁴⁾. The gene *BRCA2* has 27 exons and encodes for a 3,418 amino acid protein. Mutations in the *BRCA2* gene are present in families with an elevated of breast cancer incidence and also have been found to be involved in MBC ⁽⁴⁵⁾. A low androgen level is, however, a popular MBC's risk factor ⁽⁴⁶⁾. Contrary to female breasts, anecdotal information suggests that male breasts are presumed in an entirely anatomical sense with little emotional or sexual affiliation ⁽²⁰⁾.

MBCs are often usually low grade, and mostly hormone receptor–positive ⁽¹⁸⁾. Despite less than 1,500 new cases identified every year in the U. S., our awareness and remedial methods for MBC are usually derived from our understanding of Female Breast Cancer. After all, if men and women breast cancer are all the same mechanism for the disease, we may predict identical occurrence outcomes ⁽⁴⁷⁾. Structural genomic rearrangements seem to be usual in both male and female breast cancer patients ⁽⁴⁸⁾. Evidence on Female Breast Cancer suggests that changes in some tumor suppressor genes and oncogenes play a significant work in breast cancer growth and enhancement ⁽⁴⁹⁾. Knowledge on MBCs and its psychological and physical effect is lagging behind.

V. ROOT CAUSES

The development of MBC has involved both environmental and genetic factors. A common factor among most but not all of these situations seem to be a change in the hormonal levels, defined by enhanced estrogens production or availability or lower testosterone levels. That definition is underpinned by the reality that breast is a terminal organ responsive to oestrogen. With hormonal imbalance, potential for malignant transformation ⁽⁵⁰⁾. Foremost breast cancers have been identified in male patients with prostate cancer who received estrogen treatment ⁽⁵¹⁾. Hormonal disorder is one of the root causes of MBC. Many anomalies with possible effect on testosterone output and high breast cancer risk involves testis without descending and the occurrence of mumps orchitis at the time of adulthood ⁽⁵²⁾. Quite apart from the extensive correlation among hormonal disorders and MBC progression, it remains unclear if levels of testosterone are genuinely affected at diagnosis ^(50 - 53). A variety of external factors have been related to breast cancer in men. Steel workers and other professions that get exposed to extremely high temperatures had recorded rises in breast cancer, likely due to decrease in the output of testosterone levels ⁽⁵⁴⁾. Geographic regions have higher incidence rates of MBC recorded in Africa and Egypt comparison to mild climate regions ⁽⁵⁵⁾. Obesity leads in higher peripheral transformation of testosterone to estrogens, so abnormal food habits or obesity due to any other reason may be responsible breast cancer prevalence ⁽⁵⁶⁾. Excess adipose tissue in obese men creates an environment favorable to higher production of estrogen. Indeed, obese male generate as high as 2 times more estrogen than male with average BMI and men with very high BMI (almost 35) show significantly

reduced levels of testosterone and increased levels of estradiol in blood plasma⁽⁵⁷⁻⁵⁸⁾. Thus, weight gain combined with the decreasing hormone levels of in the elderly men may provide a hormonal environment that helps facilitate the evolution of Male Breast Cancer in overweight and obese male⁽⁵⁹⁾. Electromagnetic fields exposure has made the breast carcinoma and other cancers more controversial. There is no definitive evidence to date that suggests this environmental factor in the progression of breast cancer, while electricians and telecommunication staffs may seem to be at an elevated risk of cancer⁽⁶⁰⁾. Patients with Klinefelter's syndrome have a 20 to 67 times greater incidence of breast cancer^(18, 28). The patients of this syndrome have altered hormonal metabolism with reduced levels of testosterone⁽⁶¹⁾. Several other genetic changes that significantly raise the breast cancer's risk in women (e.g. RAD51C, BRIP1) were not linked with an increased breast cancer risk in men⁽⁶²⁾. With the increasing age, the risk of advancement of breast cancer also increases⁽⁶³⁾. In females with history of premature ovarian and breast cancer are related to BRCA gene on chromosome 17q, breast cancer in men is rarely reported to have in family history with BRCA1 mutation⁽⁶⁴⁾. In pedigrees with a particular intensity of Female Breast Cancer, correlation towards the more recently developed BRCA2 locus on chromosome 13q also related with an increased risk of MBC in some of the family members⁽⁶⁵⁾. Studies also reported by researchers that higher levels of oestradiol and oestrone serum levels were also responsible for MBC⁽⁶⁶⁾.

VI. TREATMENT

Modified radical mastectomy is the most common form of Male Breast Cancer surgery. Research from the series of cases involving Male Breast Cancer suggests that radical mastectomy is modified be used in somewhat 70 percent of patients, accompanied by radical mastectomy (8 to 30 percent), complete mastectomy (5 to 14 percent), and lumpectomy both along with or without radiation (1 to 13 percent)⁽⁶⁷⁻⁶⁹⁾. Breast cancer chemotherapy can be cytotoxic or endocrine in its medical applications, with gender-different negative effects and conclusions. Cytotoxic chemotherapy for MBC, remains a poorly researched subject in both the adjuvant and neoadjuvant situations. There is a small basis for testimonials indicating that the adjuvant chemotherapy reduces the relapse rates in MBC, but these treatments are now less commonly used in male diseases compared with similar female breast cancers patients matching age and disease progression⁽⁷⁰⁾. The HER2 down regulator, Trastuzumab, has proved to be a successful element of the female breast cancer treatment armory. However, its role in MBC is less exonerated, because the HER2 receptor tends to be overestimated less often than not associated with female breast cancers⁽⁵⁷⁾. As with chemotherapy, radiotherapy in MBC has a lack of data to guide the development of appropriate treatment schedules. The therapy is widely used in MBC, in contrast to more efficient use in female disease, as the male breast tissue renders a smaller volume, makes it a challenge to achieve comfortable surgical margins⁽⁷¹⁾. Radiotherapy is linked with substantial pulmonary and cardiovascular morbidity, reducing its utility in the aging MBC patient's population⁽⁷⁰⁾. Hormonal therapy seems to be the first-line cure with cytotoxic chemotherapy as second-line treatment for metastatic MBC. Hormonal therapy was previously performed medically by way of adrenalectomy, hypophysectomy, or orchidectomy. These strategies were successful in 55 to 80 percent of cases but agonized and bore their own morbidity⁽⁷²⁾.

The medicine Tamoxifen has been widely used as adjuvant therapy for female breast carcinoma. Although individual patients with MBC might have been adjuvant to Tamoxifen, no recorded report has been released on

the effectiveness of Tamoxifen used as adjuvant therapy in the patient population to the author's experience. The explanation for this is the obvious one, the prevalence of the disease ⁽⁷³⁾.

VII. FUTURE PERSPECTIVES

Despite improved diagnosis, screening, and treatment, cancer remains a significant danger to our society ⁽⁷⁴⁾. The planet's population is estimated to be 7.5 billion by 2020, with an extra 15.0 million by 2020. more new cases of cancer events will be identified; around 12.0 million cancer victims will have a decline in their existence ⁽⁷⁵⁾. Since the usage of powerful-throughput technology, vast knowledge has become accessible for medical research at different rates, such as genomics, transcriptional, translational and epigenetics. Rising effort have been made to incorporate knowledge at various levels in order to understand the core differential expression that cause the heterogeneity of breast tumors and to pursue successful treatment ⁽⁷⁶⁾.

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