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## RESEARCH ARTICLE

# AZOOSPERMIA IN SUDANESE MALES WITH BREAST CANCER: A MULTIPLE CASE REPORT

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**ABSTRACT**

**Background:** Male breast cancer (MBC) is an uncommon rare medical condition that is responsible for about 1% of all the malignancies in men as well as for 1% of all of breast carcinoma. Nearly all of the men with breast cancer do not have any distinguishable risk factors. The majority of males with breast cancer presents at older ages as opposed to females with breast cancer.
**Case presentation:** Twenty three cases of MBC, diagnosed between October 2011 and September 2014. Azoospermia was found in eighteen patients, and five patients had oligospermia. For azoospermic MBC patients additional biochemical markers were done (Total testosterone, Follicle-stimulating hormone and total cholesterol) before starting treatment.
**Results:** Follicle-stimulating hormone as well as cholesterol levels were significantly increased in MBC patients when compared to control group, whereas total testosterone level was decreased insignificantly in MBC patients.
**Conclusion:** In this study, the results suggested that the presence of azoospermia increased the chance to develop breast cancer by a mutual mechanism which affects the function of androgen receptors.



## INTRODUCTION

Male breast cancer (MBC) is an uncommon medical condition that is responsible for about 1% of all the malignancies in men as well as for 1% of all of breast carcinoma (**Eisenberg *et al*., 2013**). According to **The American Cancer Society, in 2012**, 2190 new cases of invasive breast cancer are going to be identified in males together with 410 men will perish of breast cancer. Male breast cancer (MBC) requires remarkable awareness to boost instant detection coupled with the establishment of proper treatments. As a consequence of poor clinical acuity and even low apprehension in men with breast warning symptoms, breast cancer is generally detected at later stages, with no less than 50% the patients presenting with stage two or maybe even higher breast cancer. It would not be unusual afterward that around 50% of cases come with regional spread of cancer to the axillary lymph nodes at the time of diagnosis. Increased estrogen exposure or androgen inadequacy can predispose men to breast cancer. The nearly all of the men with breast cancer do not have any distinguishable risk factors. In the prospective National Institutes of Health-AARP Diet and Health Study, 324.920 men were evaluated, among whom 121 developed breast cancer. The risk was considerably greater in men who had a first degree relative with breast cancer (RR 1.92), a history of a bone fracture after age 45 (RR 2.2), obesity (RR 1.79) as well as reduced levels of physical exercise (**Brinton *et al*., 2008**). Testicular disorders linked to an increased likelihood of MBC include undescended testes, congenital inguinal hernia, orchiectomy, orchitis, and additionally infertility. To date, there is no substantial proof to link gynecomastia with MBC, nevertheless is likely to be connected as a result common hormonal risk factors (**Fentiman *et al*., 2006**).

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### Case Presentation, Materials and Methods

This study was carried out in Khartoum state, in the Radiation and Isotopes Center Khartoum (RICK) and Khartoum Oncology Specialized Center (KOSC) between October 2011 and September 2014. The study included 23 male patients with breast cancer with clinical and histopathological evidence and 23 normal healthy volunteer males as control group. All patients presented with symptoms suggestive of MBC as nipple discharge, breast swelling, nipple retraction, and skin dimpling, for duration ranged between six months and one year. Diagnosis was confirmed by mammography as well as core needle biopsy and before the commencement of standard treatment. All patients experienced no signs of metastasis to local axillary lymph nodes or distant organs. They experienced a different cultural background and all of them with no history of smoking or biochemical evidence of diabetes, hormonal

disorders, high blood pressure, renal or liver disease or family history of chest malignant neoplastic disease.

Informed consent was obtained from each participant. Pre-prepared questionnaire including data concerning patients and their breast cancer information (such as age, family history, type of treatment, and BMI) was used. This study was approved by the ethical committee of Omdurman Islamic University. Seminal fluid and blood samples were collected from each participant. Seminal fluid was collected by masturbation technique as described by (**Kathiresan *et al*., 2012**) and analyzed immediately by computer-assisted sperm analysis (CASA) system as described by (**Tomlinson *et al*., 2010**). Venous blood sample (10 ml) was obtained at 8:00-10:00 AM from antecubital vein after an overnight (for 10 hours) fasting from patients and controls by standard venipuncture technique without venous stasis, in serum separator tube. Serum was separated after 20 minutes and then stored at -20°C for less than 3 weeks till the time of analysis. Then, serum levels of total cholesterol, total testosterone and FSH were measured. Total cholesterol level was measured by standard laboratory method on a Hitachi 912 Chemistry Analyzer (Roche Diagnostics, Germany) as described by (**Shi *et al*., 2014**). Serum total testosterone and follicle-stimulating hormone (FSH) levels were determined by a chemiluminescent assay as described by (**Guo *et al*., 2014**). All statistical analyses were carried out using a commercially available statistical package SPSS version 12.0. Values of $p<0.05$ were considered statistically significant.

## RESULTS

Azoospermia was found in 18 patients and oligozoospermia in 5 patients. The study included 18 MBC patients in age of 49.1 ± 4.5years and BMI of 23.2 ± 8.3, and 23 volunteers matching in age (47.3 ± 6.3years) and BMI (24.8 ± 7.5) as a control group. The results of semen analysis showed normal volume, normal pH, and significant increasing in white blood cells count comparing to the control group. While the blood biochemistry results when compared to the control group showed normal level of total testosterone and significant increase in both results of FSH and total cholesterol.

**Table 1. Demographic data, Seminal Analysis, and Biochemical test results in MBC patients with azoospermia**

| Parameters | MBC Patients with azoospermia | Control | P value |
|---|---|---|---|
| Number | 18 | 23 | - |
| Age (years) | 49.1 ± 4.5 | 47.3 ± 6.3 | 0.19 |
| BMI | 23.2 ± 8.3 | 24.8 ± 7.5 | 0.21 |
| Seminal Analysis: | | | |
| Volume | 4.4 ml (ranged between 3 - 8 ml) | 3.9 ml (ranged between 1.8 – 4.6ml) | 0.071 |
| Seminal pH | 7.25±0.23 | 7.41±0.17 | 0.128 |
| White blood cells count | $2.018\times10^6$/ml | $0.893\times10^6$/ml | 0.000 |
| Biochemical results: | | | |
| Total Testosterone (ng/dL) | 572.97±22.1 | 634.1±41.9 | 0.054 |
| FSH | 21.75 ± 10.4 mIU/ml | 8.82 ± 9.27 mIU/ml | 0.000 |
| Total cholesterol (mg/dl) | 247.3± 40.11 | 153.6 ± 1.5 | 0.002 |

## DISCUSSION

This work suggests that azoospermia increases the chance of MBC. Among 23 patients with MBC, 78.3% had azoospermia and the other 21.3% had oligozoospermia. This finding strongly suggests a relationship between defective spermatogenesis and MBC. Patients were not aware of the presence of azoospermia until diagnosed in this study. Although some of the patients were married, all of them had no children. The result is generally consistent with a previous study found that the presence of azoospermia before age 30 conveys an eight-fold cancer risk (**Eisenberg *et al*., 2013**). To our knowledge, the present study is the first which proposes a relationship between azoospermia and the growth of breast cancer in men. For both azoospermia and male breast cancer, there may exist a common genetic mechanism that results first in azoospermia, and later on an unidentified point of time, the same mechanism causes MBC. This mechanism may be related to Androgen Receptor (AR) abnormalities.

AR is a nuclear receptor that transforms into activated status when binds to androgens, such as testosterone and dihydrotestosterone, and consequently facilitates the transcription of certain genes in the cell which related to the natural development of the male sexual characteristics (**Heinlein *et al*., 2002**). Androgen as well as the AR executes crucial tasks in male spermatogenesis and fertility. At the same time, the non-existent of AR in Sertoli cells disturbs the ability of Sertoli cell to sustain and nourish germ cells, which in turn results in spermatogenesis apprehension (**Wang *et al*., 2009**). On the other hand, the presence of AR mutations has been described in MBC along with the accompanied reduction in androgen action within the breast cells would possibly give reason for the development of male breast cancer (**Lobaccaro *et al*., 1993**). We could not correlate the normal level of testosterone in those 23 patients with AR genetic mutations. In a single study, testosterone levels were increased in males with AR mutations, but then again, the levels were not conclusive and overlapping (**Ferlin *et al*., 2006**).

Androgen Insensitivity Syndrome (AIS) also worth mentioning here because it's related to androgen receptors. AIS is a condition that results from AR mutations (**Quigley *et al*., 1995**). More than 400 AR mutations have already been reported (**Galani *et al*., 2008**).

Although the insensitivity to androgens is clinically significant only when it occurs in genetic males, some of its clinical variant's presented with normal male habit us with mild spermatogenic defect; Mild Androgen Insensitivity Syndrome

(**Ferlin *et al*., 2006**). The cases are also suggestive of Klinefelter syndrome, which associated with Elevated follicle stimulating hormone (FSH), luteinizing hormone (LH) and estradiol, and low to low-normal testosterone level. In one study, Hypercholesterolemia was documented in 56.6% of Klinefelter patients (**Lichiardopol *et al*., 2004**).

We could not relate the time period of symptoms and signs ahead of MBC detection in those patients with the onset of azoospermia, mainly because the diagnosis of both conditions was simultaneous.

**Conclusion**

MBC associates with many risk factors: azoospermia, and to lesser extent oligospermia, could be one of them, and early analysis of semen in a young healthy males may reveal a possibility of breast cancer development as well as providing early intervention. Other possibilities that may explain the presence of azoospermia in MBC include Mild Androgen Insensitivity Syndrome, Klinefelter syndrome. More efforts should be conducted to separate these entities, and more studies are needed to evaluate the situation.

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