Breast Cancer in a Filipino Male: A Case Report and Brief Literature Review

Jose Ma. H. Zaldarriaga, MD, MBA, Aldric Mikhail N. Aw, MD, Gaudencio P. Vega, MD, Angela Gaerlan-Tagle, MD, Angela Pena-Camacho, MD and Juan Martin J. Magsanoc, MD

Department of Radiation Oncology, St. Luke's Medical Center-Quezon City

ABSTRACT

This is a case report of a 76-year-old Filipino male who presented with a six-year history of a steadily growing left breast mass. The mass was eventually diagnosed to be Invasive Ductal Carcinoma, Anatomic and Prognostic Stage IIIB (T4b cN0 M0), Grade 3, Luminal A. Subsequently, the patient underwent neoadjuvant chemotherapy of doxorubicin/cyclophosphamide and paclitaxel, followed by modified radical mastectomy with axillary lymph node dissection, concluded by post-mastectomy radiation therapy. The patient had complete clinical response to this trimodality therapy.

The rarity of this case is juxtaposed and integrated with the present literature on male breast cancer.

Keywords: male breast cancer, oncology, invasive ductal carcinoma

CASE PRESENTATION

This is a case of a 76-year-old Filipino male, previously healthy with no known comorbidities, who in 2015 noted a marble-sized, irregularly-bordered, nonmobile, nontender mass in the retro-areolar area of his left breast. No bleeding, no discharge, nor other subjective complaints were noted at this time. For the next six years, the mass was noted to gradually but steadily increase in size, becoming fungating and nodular, and eventually ulcerating the overlying skin and nipple-areola complex. In August of 2021, upon urging by his family, the patient finally sought consult at our institution. On presentation, a 6.5 x 6.0 x 3.0 cm irregularly bordered, firm, fungating, nodular, nontender, nonmobile mass was seen overlying the nipple-areola complex of the left breast. No discharge nor bleeding was noted from the mass (Figure 1). There were no palpable enlarged or suspicious lymph nodes.

Past medical and family history of the patient were unremarkable. He is a 30 pack-year smoker and occasional alcohol beverage drinker. He denies taking any hormonal medications, illicit substances, complementary and alternative medicine (CAM) preparations, or herbaceuticals. He has no previous history of radiation. There is no known history of any malignancy nor genetic syndromes in the nuclear or extended family. Now retired for more than 20 years, the patient used to be an active tricycle driver.

Breast ultrasound was performed, revealing a large, lobulated, heterogenous mass at the retroareolar area, measuring 5.4 x 3.6 x 5.7 cm, BIRADS Category 5. No

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Corresponding author: Jose Ma. H. Zaldarriaga, MD, MBA
Department of Radiation Oncology
St. Luke's Medical Center-Quezon City
279 E. Rodriguez Sr. Avenue, Quezon City, 1112 Philippines
Email: radoncocensus@gmail.com
ORCiD: https://orcid.org/0000-0003-3631-6317

discrete mass lesion was noted in the right breast. Likewise, bilateral axillary areas revealed no suspicious nodes, masses, nor any abnormalities. This was corroborated by a digital mammography which similarly revealed an irregular, high density mass at the retroareolar region of the left breast, approximately measuring 4.3 x 6.7 x 6.0 cm, with associated architectural distortion, thickened skin line, and nipple retraction (Figure 2).

A core needle biopsy of the left breast mass revealed invasive breast carcinoma of no special type, with Nottingham histologic grade 3, and no definite lymphovascular invasion. The tumor was Estrogen receptor positive (strong staining, 100% of cells), Progesterone receptor positive (strong staining, 90% of cells), Androgen receptor positive (strong staining, 90% of cells), Ki-67 positive (70%), and HER-2/neu negative.

Subsequently, whole abdominal CT scan, and chest and mediastinum CT scan were performed as part of metastatic workup, revealing unremarkable findings.

As such, at this point prior to any treatment, the patient was staged as Anatomic and Prognostic Stage IIIB (T4b cN0 M0), Grade 3, ER+, PR+ HER2-.

The patient then received neoadjuvant chemotherapy composed of doxorubicin/cyclophosphamide followed by paclitaxel (4 cycles of doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2 every 21 days; 4 cycles of paclitaxel 175 mg/m^2 every 21 days).

After chemotherapy, the mass had decreased in size, now 6.7 x 5.0 x 2.1 cm, still irregularly bordered, firm, fungating, nodular, nontender, and nonmobile. Post-neoadjuvant therapy, the malignancy was still Anatomic and Prognostic Stage IIIB (T4b cN0 M0). One month after the last cycle of chemotherapy, the patient underwent modified radical mastectomy with axillary lymph node dissection, with the following pertinent histopathologic features: tumor size of 7 cm in greatest dimension with ulceration of overlying skin, negative margins, invasive ductal carcinoma, Nottingham histologic grade 3, and no lymphovascular invasion. In addition, none of the 14 harvested axillary nodes were positive for tumor. Pathologically, the Anatomic and Prognostic Stage of the patient was still IIIB.

A month after the surgery, the patient was then referred for postmastectomy radiation therapy. By this time, the mastectomy scar was already well-healed and coaptated. The patient was prescribed a dose of 5000 centi-Gray in 25 fractions, Mondays to Fridays, to the right chest wall, right axillary levels I, II, and III, right supraclavicular fossa, and right internal mammary chain. The radiation was delivered via opposing tangential fields via a field-in-field (FIF) technique, using 6-mega voltage (MV) photons. Thereafter, the patient was prescribed a scar boost of 1000 centi-Gray in 5 fractions, using 6-mega electron volts (MeV). Aside from hyperpigmentation of the right chest wall and right axilla (Figure 3), there were no other observed toxicities. The treatment was generally well-tolerated.

Follow-up

Follow-up six months post-radiation therapy revealed the patient to be well and asymptomatic. There were no visible nor palpable masses or nodularities in the right chest wall nor axilla. The previously noted hyperpigmentation has now completely resolved. He was then started on daily tamoxifen for a total duration of five years.

Twelve months post-radiation therapy, the patient continues to be well and asymptomatic. A chest CT scan with IV contrast was done as part of treatment monitoring, proving to be unremarkable with no lesions suggestive of residual nor recurrent disease.

DISCUSSION

Male breast cancer is a rare disease with potentially distinct biological and clinical differences compared to its more common female counterpart.[1] It accounts for less than 1% of all breast cancer cases[2,3], less than 1% of all male cancers[4-6], and less than 0.1% of all cancer deaths in men.[7]

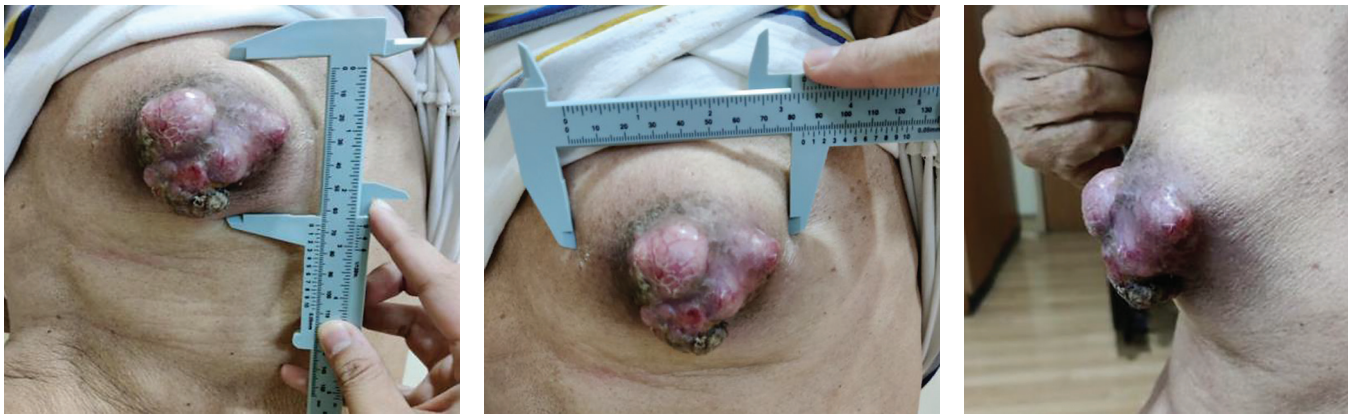

Figure 1. The 8.0 x 6.5 x 3.0 cm irregularly bordered, firm, fungating, nodular, nontender, nonmobile mass overlying the nipple-areola complex of the left breast seen on initial consult.

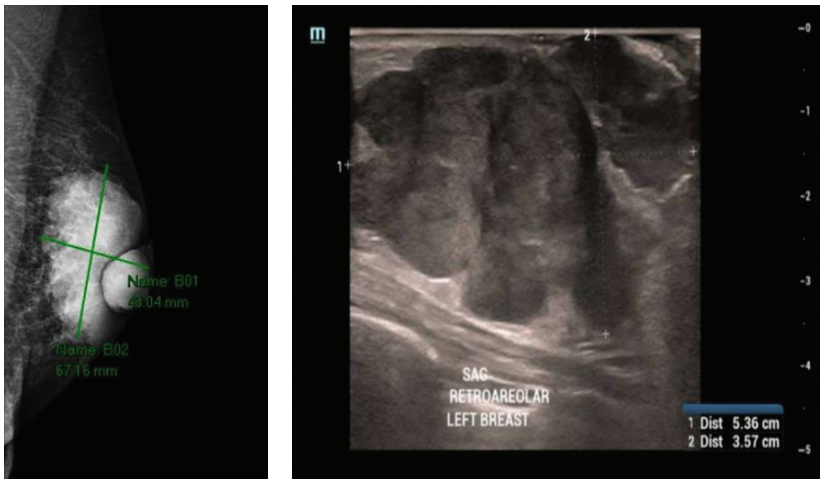

Figure 2. The large, lobulated, heterogenous mass at the retroareolar area, as visualized via 2D breast ultrasound and digital mammography.

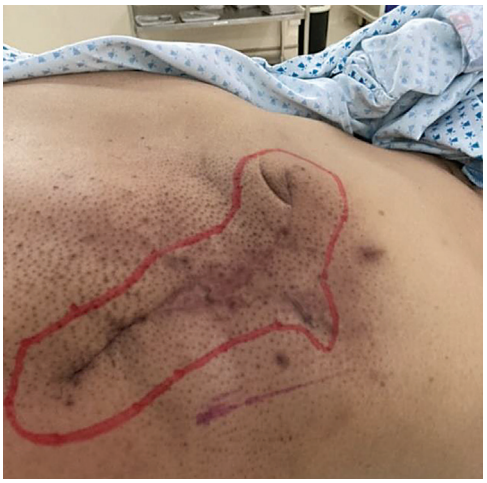

Figure 3. Hyperpigmentation with no desquamation over the right chest wall at the time of the scar boost.

In women, the age frequency distribution of breast cancer is bimodal, peaking at 52 and 71 years of age; in men, it is unimodal, peaking at 71 years of age.[8]

The geographic distribution of male breast cancer varies widely. In parts of Africa, specifically Uganda and Zambia, the annual incidence rates are 5% and 15%, respectively. These relatively high rates are posited to be secondary to endemic infectious diseases causing hepatic damage which in turn leads to endogenous hyperestrogenism.[9,10] In contrast, Japan has among the lowest incidence rates of less than five per million, in parallel with the likewise lower than average female breast cancer incidence in the country.[11] To the authors' knowledge, in the Philippines, no published data on male breast cancer incidence and prevalence yet exists.

Several risk factors for the development of male breast cancer have been identified; broadly, they can be categorized into genetic, disease-related, lifestyle-related, and occupational factors. A family history of breast cancer confers a relative risk of 2.5[3]; 20% of men with breast cancer have a first-degree relative with the disease[12]. However, we note that our patient has no such family history, at least to his knowledge. Among women, 5-10% of breast cancers are posited to be due to autosomal dominant inheritance of BRCA1 and/or BRCA2 mutations.[13] Among men, the figure is estimated to range from 4% to 40%. Specifically, male breast cancer is more significantly associated with BRCA2 than BRCA1 mutations.[14] The role of genetics in male breast cancer is likewise evident among patients with Klinefelter's syndrome, a genetic disease characterized by the addition of at least one X chromosome to the normal XY karyotype in males. Clinically, it is exhibited by testicular dysgenesis, gynecomastia, hypotestosteronemia, and increased gonadotrophins. The risk of breast cancer in males with Klinefelter's syndrome is 20 to 50 times higher than their female counterparts.[15,16]

Certain diseases have also been implicated as risk factors for male breast cancer. Liver damage such as secondary to cirrhosis or hepatocellular carcinoma is associated with increased estrogen levels which in turn has been implicated in breast cancer.[17,18] Diseases associated with testicular abnormality or damage have likewise been associated with male breast cancer. Such include cryptorchidism, testicular mumps, and unilateral or bilateral orchiectomy, all of which are associated with hypoandrogenemia and consequent hyperestrogenism.[19,20] Prior radiation therapy to the chest area, such as for lymphoma and, historically, for benign conditions such as gynecomastia, thymic hypertrophy, and eczema, has likewise been found to increase the risk of male breast cancer by 1.6 to 1.9 times.[21,22] Again, we note that the past medical history of our patient is unremarkable.

There are several lifestyle factors found to have an association with male breast cancer. Exogenous estrogen has been found to be a significant risk factor, as seen in men being treated for prostate cancer and transsexuals who are taking estrogens.[23,24] A more common lifestyle-related factor implicated in male breast cancer is obesity, one of the most common causes of hyperestrogenism in males,[12,25,26] which can increase its risk by as much two times[27]. Alcohol consumption is another factor associated with male breast cancer.[28,29] A recent European multi-center case control-study found that the risk of male breast cancer rose by 16% per 10 g daily alcohol intake.[29] Of these risk factors, we recall that our patient is an occasional alcohol drinker, possibly increasing, no matter how modestly, his risk for breast cancer.

Finally, in terms of occupational factors, interestingly, an increased frequency of male breast cancer was reported among those working in hot environments such as steel works, blast furnaces, and rolling mills.[30,31] Occupational exposure to exhaust fumes and petrol has likewise been implicated, the presumed carcinogens being polycyclic aromatic hydro-

carbons (PAH) which are present in exhaust emissions and tobacco smoke.[32,33] We recall that our patient was a former tricycle driver – an occupation particularly exposed to exhaust fumes. He was likewise a chain smoker. Both of these factors could have potentially significantly increased his risk for developing this uncommon disease.

Similar to breast cancer in females, the most common symptom of male breast cancer is a painless lump.[34-37] Nipple involvement - involving retraction, inversion, edema, and/or eczema- is often an early event, seen in 17-30% of patients.[21,38,39] These findings were similarly noted in our patient. Because the male breast tissue is rudimentary, it does not typically differentiate and undergo lobule formation unless exposed to increased estrogen levels. As such, the majority-(90%) of all male breast cancers are invasive ductal carcinoma.[40-42]

Due to the disease's rarity, very few male patients have been included in breast cancer trials. There is, to date, no dedicated randomized controlled trial exclusive for male breast cancer patients. Our data on management strategies, outcomes, and prognoses are derived from case reports, series, and retrospective reviews.[43] As such, guidelines on the management of male breast cancer have generally simply been extrapolated from those for its more common female counterpart. For our patient, neoadjuvant systemic therapy was utilized due to the cT4b stage and relatively large tumor size, likewise making the subsequent surgery more technically feasible.[1,44,45]

To date, majority of the surgical management of male breast cancer is modified radical mastectomy (MRM),[46-50] as was done with our patient. However, there is increasing data suggesting that, for early-stage male breast cancer, breast-conserving surgery (BCS) is associated with locoregional control, survival, and safety outcomes that are equivalent to those of mastectomy.[49-52] Similarly, limited case series and single-institution experience indicate that, in the setting of male breast cancer with a clinically node-negative axilla, sentinel lymph node biopsy (SLNB) stages the axilla as accurately as axillary lymph node dissection (ALND) minus the concomitant morbidity associated with the latter.[47,49,53] As such, the NCCN recommends that the same criteria for selecting between breast conservation versus mastectomy as well as surgical axillary staging as applies to female breast cancer be applied to male breast cancer cases as well.[1]

Adjuvant radiotherapy has been delivered proportionally more frequently to male compared to female breast cancer cases, largely because a greater proportion of male breast cancer is diagnosed at a more advanced stage.[54] Eggeman et al. found a statistically significant benefit in overall survival (OS) for stage III male breast cancer patients treated with adjuvant radiotherapy compared to those who were not (10-yr OS = 26.4% vs 11.9%, $p < 0.05$).[55] In a study by Abrams et al. of the Surveillance, Epidemiology, and End Results Program (SEER) database, among 315 cases matched by age, race, ER status, T-stage, N-stage, and histologic grade, adjuvant radiotherapy was again found to provide a statistically significant benefit in OS (5-yr OS = 83% vs 54%, $p < 0.001$).[56] These and similar other retrospective studies found that the locoregional control and survival benefit provided by adjuvant radiotherapy was more pronounced for tumors larger than 5 cm[55-57], at least one positive node[56,57], and close or unknown margins[58]. As such, stage by stage, the indications for adjuvant radiotherapy appear to be similar for male and female breast cancer.[17] Hence, the NCCN recommends adjuvant radiation for male breast cancer based on the same criteria as is used for female breast cancer.[1] For our patient, the tumor size, skin ulceration, and grade are high-risk recurrence factors which make pursuing adjuvant radiation more prudent.

As with the case of our patient, more than 90% of male breast cancer is ER+ and PR+, strongly supporting the role of adjuvant hormonal therapy, specifically tamoxifen.[36,59,60] Although there are no clinical trials supporting the use of tamoxifen in male breast cancer, several retrospective reviews have found locoregional control and survival benefits. Ribeiro and Swindell found a 17% improvement in 5-year overall survival among 39 male breast cancer patients with Stage II-III disease who were treated with a 1-2-year course of tamoxifen compared to those who were not.[59] A similar study by Goss et al. noted improved disease free- and overall survival rates with the use of tamoxifen.[60] Of note, however, is that clinical trials in female breast cancer have shown that the optimal length of tamoxifen use for hormone-sensitive disease is five years. As such, these studies may actually even be underestimating the benefit of tamoxifen in male breast cancer. Our patient was prescribed daily tamoxifen for a total of five years adjuvantly.

Due to the rarity of male breast cancer and, therefore, the low index of suspicion for patients and physicians alike, the disease is notoriously associated with a delay in diagnosis. The estimated mean delay is 6-10 months.[36,61] For our patient, we recall that it took him six years to seek consult, when the breast mass is already grossly visible and fungating. As a result, more than 40% of male breast cancer is diagnosed at Stage III-IV, thus lending an overall worse prognosis compared to female breast cancer.[59-61] However, when adjusted for age and stage, the survival rates are statistically similar.[17,62,63] Combined estimates of 5-year overall survival rates, adjusted for age and stage, for male vs female breast cancer, are 96% vs 99% for Stage I, 84% vs 84% for Stage II, 52% vs 55% for Stage III, and 24% vs 18% for Stage IV.[17,51,62,63]

CONCLUSION

Given its rarity, the general approach to and treatment strategy for male breast cancer is largely patterned after those for its more common female counterpart. Our patient's management was, in huge part, based upon the guidelines developed from and most commonly applied towards female breast cancer. There is, however, mounting evidence that male breast cancer may be a distinct disease entity, possibly

with key anatomical, biological, and clinical differences. Our knowledge on this rare disease is yet evolving and it is not surprising for clinical guidelines for male breast cancer to evolve in the coming years in the face of emerging data.

Statement of Authorship

JMHZ and AMNA contributed in the conceptualization of work and drafting and revising of manuscript. GPV and APC contributed in the conceptualization of work and final approval of version to be published. AGT and JMJM contributed in the drafting and revising of manuscript and final approval of version to be published.

Author Disclosure

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