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A Male Patient Diagnosed with HER-2 Negative Breast Cancer and Brain Metastasis: A Case Report

Paciente masculino con diagnóstico de cáncer de mama HER-2 negativo y metástasis cerebral: reporte de caso

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SUMMARY

Globally, Male breast cancer (MBC) is a rare condition, and the literature is elusive. Advanced cases lead to metastases, including brain metastases (BMBC). A 55-year-old male experienced a loss of consciousness and trouble raising his right arm. A painless lump on the right breast was 5 cm in diameter. The patient underwent a modified radical mastectomy. Tissue biopsy showed invasive ductal carcinoma, ER+, PR+, HER-2-, and Ki67+. Brain MRI depicted contrast enhancement in the right subcortical frontoparietal lobe. The patient died from septic shock due to recurrent pneumoniae. The patient received treatments according to established guidelines. However, BM still developed within 20 months. This is considered a distinct phenomenon since HER-2+ BC commonly causes BMBC. Underlying mechanisms might be due to different signaling pathways. Although MBC shows many similar aspects to female breast cancer (FBC), distinctive characteristics should be the genesis of further discussion.

Keywords*: Male, breast, cancer, brain, metastases, HER-2 Negative***.**

RESUMEN

A nivel mundial, el cáncer de mama masculino (MBC) es una enfermedad poco común y la literatura al respecto es escasa. Los casos avanzados conducen a metástasis, incluidas metástasis cerebrales (BMBC). Un hombre de 55 años experimentó pérdida de conciencia y dificultad para levantar el brazo derecho. Presentaba un bulto indoloro en la mama derecha, de 5 cm de diámetro. El paciente se sometió a una mastectomía radical modificada. La biopsia de tejido mostró carcinoma ductal invasivo, ER+, PR+, HER-2- y Ki67+. La resonancia magnética cerebral mostró realce de contraste en el lóbulo frontoparietal subcortical derecho. El paciente murió de choque

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séptico debido a neumonías recurrentes. El paciente recibió tratamientos de acuerdo con las pautas establecidas. Sin embargo, aún desarrolló BM dentro de los 20 meses. Esto se considera un fenómeno distinto ya que el cáncer de mama HER-2+ comúnmente causa BMBC. Los mecanismos subyacentes podrían deberse a diferentes vías de señalización. Aunque el cáncer de mama metastásico muestra muchos aspectos similares al cáncer de mama femenino (FBC), las características distintivas deberían ser el origen de un debate más profundo.

Palabras clave*: Cáncer, mama, masculino, cerebro, metástasis, HER-2 negativo.*

INTRODUCTION

To date, breast cancer (BC) is one of the most frequent types of cancer detected in women but not in men. Male breast cancer (MBC) is diagnosed in only 0.5 %-1 % of all BC cases worldwide (1). According to Surveillance, Epidemiology, and End Results (SEER) data, the incidence of MBC increased by 40 % from 1975 to 2015 (2). GLOBOCAN 2020 states that breast cancer in Asia accounts for 10.8 %, with no exact data showing the prevalence of MBC (3). In Indonesia, BC ranks the highest number of new cases with the second highest mortality rate, after lung cancer. Data regarding MBC in Indonesia are not yet mentioned (3).

Little is known about the exact etiology of MBC. Different risk factors have been associated with developing breast cancer in men, including obesity, family history of breast cancer, black race, and exposure of the breast to ionizing radiation, among others; however, the two most significant factors that have been described are carrying a diagnosis of Klinefelter's syndrome and having a predisposition germline genetic mutation (BRCA2, BRCA1, CHEK2, PALB2). Hormonal, environmental, and genetic factors underlie its pathogenesis. There are differences between clinical and biological characteristics of MBC and female breast cancer (FBC), such as hormone receptor (HR) and HER-2 status (4). Currently, management of MBC still refers to post-menopausal FBC since there are only a few randomized controlled trials (RCTs) on male patients (5). Moreover, when the tumors have progressed to an advanced stage, MBC patients could also end up experiencing metastases with common anatomical sites, such as bone, liver, lung, and brain. Brain Metastases of Breast Cancer (BMBC) is a challenging presentation of breast cancer, often associated with poor prognosis. Studies have demonstrated that breast cancer in men is more often Hormone Receptor (HR) positive when compared to female breast cancer, and its prevalence is similar to that in postmenopausal women, which indicates that breast cancer in men is usually responsive to anti-hormonal therapies like tamoxifen. However, the risk of brain metastases is higher in patients with HR-negative, human epidermal growth factor receptor 2 (HER-2)-positive, or triple-negative tumors. It has been shown that tumor subtype also plays a role in the median time interval from primary diagnosis to the development of brain metastases, and studies have demonstrated shorter intervals for triple-negative and HER2-positive tumors and longer intervals for estrogen receptor-positive tumors (6).

We report a male patient with HER-2-negative breast cancer progressing to brain metastases who had undergone surgery, chemotherapy, and adjuvant hormonal therapy. Authors considered it an atypical manifestation, particularly in Indonesia; hence, a comprehensive discussion is required.

Case presentation

Mr S, 55 years old, was admitted to the Emergency Room after gradually losing consciousness two days before the admission. Within three months, he found it complicated to button up his shirt and raise his right hand. He also had a fever, cough, and difficulty breathing. Previously, he had a history of a right breast lump two years before, diagnosed at the previous hospital. Initially, the lump was ± 1 cm in diameter, growing to ± 5 cm within ± 6 months. It was immobile, black in color, painful, with blood spots encircling it. The patient complained of no lump on the left nipple. The patient's cousin also had a history of a breast lump. The patient had a history of uncontrolled diabetes mellitus.

He was admitted somnolent, blood pressure 90/60 mmHg, pulse 89x/minute, oxygen saturation 92 % room air, and axillary temperature

38.2ºC. He weighed 65 kg and was 170 cm tall, with a body surface area (BSA) of 1.79 m^2 (Du Bois criteria). Head and neck examination showed slightly pale conjunctiva. A wound scar was seen on the right pectoral region with ± 20 cm length (Figure 1). No lumps were found around the left nipple, right, and left armpit. Crackles were heard in both lung fields. Abdominal examination revealed no organomegaly. Examination of the extremities revealed cold, dry, red extremities with positive pathological reflexes (Babinski and Chaddock reflexes) on the left side. The patient needs assistance in daily physical activities and was bedridden with a performance score (Eastern Cooperative Oncology Group, ECOG) (3).

Laboratory examination showed Hb 10.8, white blood counts (WBC) 12 450, platelets 389 000, neutrophils 80.2 %, sodium 135, potassium 2.9, albumin 2.76, and blood sugar 278. Sputum culture revealed the growth of *Escherichia coli* sensitive to ceftazidime and *Candida tropicalis* sensitive to micafungin. Urine culture showed *Klebsiella pneumoniae* sensitive to ceftazidime. Chest X-ray examination showed infected bronchiectasis and pneumoniae; no pulmonary metastases were detected. Histopathological examination following modified radical mastectomy (MRM) showed invasive ductal carcinoma, grade III, tumor diameter of 2.5 cm, 3 lymph nodes figured (T1bN2aM1) with the edges and base of the operation site free of malignant cells (Figure 2A). Immunohistochemistry presented estrogen receptor (ER) positive 15 % (weak intensity), progesterone receptor (PR) positive 30 % (weak intensity), HER-2 negative, and Ki67 positive 25 % (Figura 2B). Ultrasound of the right breast six months after MRM showed no new nodules. Head MRI with contrast depicted probable brain metastases in the right subcortical frontoparietal lobe with extensive perifocal edema, measuring 1.9x1.9x2.27 cm (Figure 3).

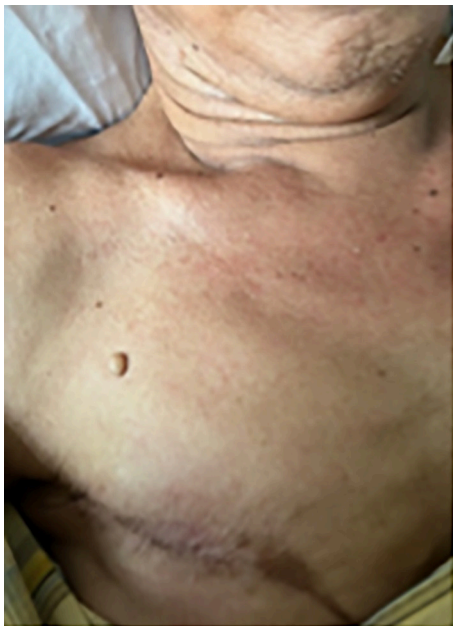

Figure 1. The post-mastectomy scar on the right breast.

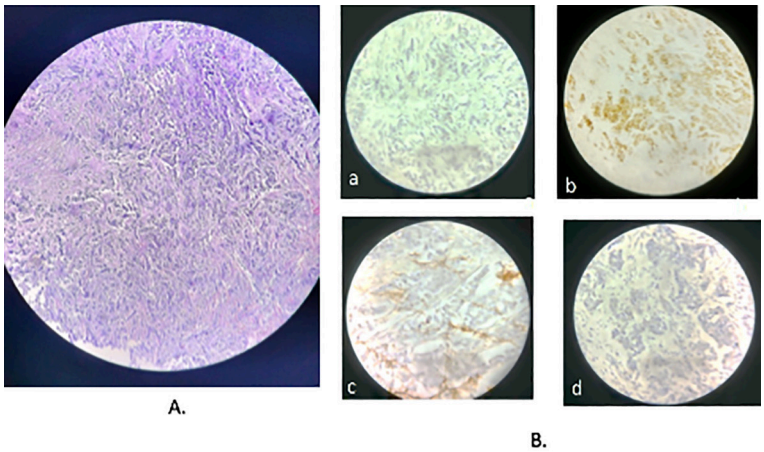

Figure 2. Additional examinations. A) Histopathology of invasive ductal carcinoma B) Immunohistochemistry staining a) Estrogen receptor; b) Progesterone receptor; c) Her2 receptor; d) Ki67 receptor.

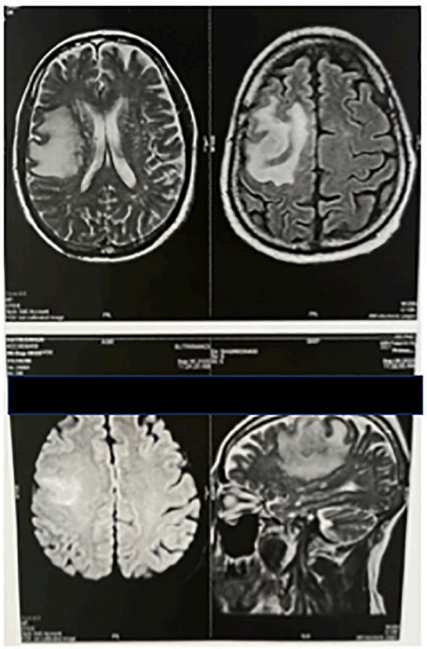

Figure 3. Contrast enhancement in the right subcortical frontoparietal lobe seen on brain MRI.

The patient was diagnosed with invasive ductal breast carcinoma T2N1M1 (Stage IV)) with brain metastases, ECOG Score 3, post-MRM, decreased consciousness due to brain metastases and septic encephalopathy, septic shock due to bacterial pneumonia and urinary tract infection, hypokalaemia, hypoalbuminemia, and diabetes mellitus (Figure 3).

At the past admission, the patient accomplished adjuvant chemotherapy comprising intravenous cyclophosphamide 800 mg and paclitaxel 230 mg for six cycles every 21 days. Oral tamoxifen 10 mg once daily was taken due to low positive hormonal receptors. During this current admission, the treatment included oxygen supplementation, intravenous fluid, enteral nutrition, intravenous mannitol QID, tapered down every two days, ceftazidime 1 gram TID, dexamethasone 5 mg every TID, micafungin 50 mg BID, paracetamol 1 gram BID, subcutaneous glargine injection 18 IU QD, and prandial Gluisin 16 U, and an extra 4 IU before dexamethasone injection. The patient was planned to receive a regimen of adjuvant chemotherapy comprising vinorelbine 50 once a week, given every 21 days, and capecitabine 1750 mg every 12 hours per day on days 1-14, every 21 days. On the fifth day of chemotherapy, his condition deteriorated. Vital signs showed BP 80/50 mmHg, pulse 122x/minute, SpO_2 92 % O_2 NRM 15 lpm, respiratory rate 30x/minute, axillary temperature 38.5ºC, with crackles in both lung fields. We proceeded with supportive therapy. The family commanded not to resuscitate (DNR). The next day, the patient underwent cardiac arrest. The patient died from a cardiovascular event and respiratory failure due to recurrent pneumoniae.

DISCUSSION

Thus far, MBC is still elusive. MBC is often diagnosed in the 50-70 age group, caused by several risk factors, such as age, hormonal, environmental (7). Hormonal factors may originate from the imbalanced estrogen-androgen in Klinefelter's syndrome, the use of exogenous androgens or estrogens, obesity, the use of finasteride, and in orchitis/epididymitis. Environmental triggers derive from radiation exposure, electromagnetic, heat, and volatile materials. BRCA2 mutations are observed in 10 % of MBC cases, more so than BRCA (1). In addition to BRCA, PALB2, androgen receptor (AR), CYP1 (7), or CHEK2 mutations can also be detected. The risk of MBC increases with a history of BC in a first-degree female relative (8). Alcohol consumption > 90 grams/day can also add up the risk of MBC by 6 times (4).

The male mammary glands are discoid in shape, 3-4 mm thick. The gland consists of adipose tissue, ducts, and connective tissue. This tissue responds to hormonal stimuli so that gynecomastia can occur and develop into cancer. The most usual clinical manifestation of MBC is a unilateral, eccentric mass located retro-areolar or paraaerolar, more often in the left breast, outer upper quadrant, and painless in its early stages (9). In some cases, the structures constructing the chest wall are involved, up to axillary lymphadenopathy. Nipple involvement is very atypical. A study stated that 57 %-75 % of MBC patients complained of bloody secretions out of the nipples (10).

Our patient was diagnosed at the age of 55 years. No hormonal imbalance, radiation exposure, or alcohol intake were recorded. The patient's cousin had a history of breast cancer. The lump appeared initially in the medial area below the right breast nipple, with an initial size of ± 1 cm, expanding to 5 cm in diameter within ± 6 months. A lump was also felt in the right armpit. The patient's nipples did not produce bloody secretions, although the adjacent lump had several bleeding spots.

Radiological examination can help establish the diagnosis of MBC. The main radiological examinations for MBC are mammography, ultrasonography, and digital breast tomosynthesis (DBT) (11). The American College of Radiology recommends ultrasonography as the initial step for male patients <25 years of age or patients with unpalpable masses. However, male patients >= 25 years old with unclear breast masses shall undergo the mammography. In this case, ultrasound can be an option if mammography doesn't work. MBC in mammography is generally described as an eccentric mass, retro auricular, with irregular edges (12).

Histopathological examination is a gold standard since it can distinguish benign from malignant breast masses (13). In this patient, tissue biopsy depicted grade III invasive ductal carcinoma, 2.5 cm in diameter, free of malignant cells on the edges and base of the operation. The expression of hormonal receptors grouped MBC into luminal A and luminal B types, where luminal A has higher expression of ER-related genes and lower expression of cells proliferation-related compared to luminal B (14). Luminal A has a higher survival rate and lower relapse risk than luminal B. Luminal type shows a better prognosis than HER-2 type. Triple-negative MBC has the worst prognosis, with only a few treatment options available (15).

Presently, surgery is considered the principal therapy for MBC. MBC surgery is divided into mastectomy and Breast Conserving Therapy (BCT) (16). Modified Radical Mastectomy (MRM) is preferred over radical mastectomy (RM) for its low invasiveness with a similar outcome as RM. Conservative Breast Surgery (CBS) followed by radiotherapy can be an alternative, although a meta-analysis states no significant difference in overall survival (OS), disease-free survival (DFS), and disease-specific survival (DSS) between mastectomy and CBS (17). According to the National Comprehensive Cancer Network (NCCN) guidelines (2023), BCT is now performed frequently in MBC with indistinguishable outcomes and safety from mastectomy (18). Our patient underwent MRM followed by adjuvant chemotherapy and endocrine therapy. Adjuvant therapy comprises chemotherapy and endocrine therapy. Considering tumor size, lymph node involvement, hormonal receptor status, HER2, and the biological profile of breast cancer itself, guidelines for adjuvant chemotherapy for MBC remain the same, as mentioned in FBC guidelines (18). Docetaxel and cyclophosphamide (TC), olaparib, pemrolizumab + carboplatin + paclitaxel for Triple Negative Breast Cancer (TNBC), or other medications are also suggested by NCCN for HER-2-. The adjuvant chemotherapy given to our patient consisted of cyclophosphamide 800 mg (dose 600 mg/m^2, BSA 1.79 m^2) and paclitaxel 230 mg (dose 175/m^2, BSA 1.79 m^2) (TC) given for 6 cycles with an interval of 21 days. This regimen was preferred since the adjuvant chemotherapy was previously executed in a smaller hospital with limited resources.

NCCN guidelines recommend tamoxifen 20 mg as the standard adjuvant endocrine therapy administered for 5-10 years (13,18). Our patient received oral tamoxifen 10 mg every 24 hours, which was planned for the next 5 years since he was intolerant to the usual dose. A cohort study of 38 patients with MBC stated that patients with adjuvant endocrine therapy had more recurrence-free and OS than those without endocrine therapy (19).

Brain metastasis (BM) occurs in 10 %-30 % of breast cancers. Brain metastases have significantly reduced life expectancy and quality of life. The most typical symptom of all types of BC is dizziness (20). Our patient began experiencing unilateral paralysis, hallucinations, and decreased consciousness since ± 1.5 years after adjuvant chemotherapy was completed. Suspicion of brain metastases was supported by brain MRI, concluding probably subcortical brain metastases in the right-fronto-parietal lobe.

Hadjipanteli et al. stated in a review that brain MRI should be considered in specific high-risk BC patients as it hopefully can detect the spread of cancer to the brain earlier. However, because brain imaging is not beneficial, current breast screening guidelines do not propose routinely assessing brain metastases (21).

BM accounts for 14 % of HR+ BC, with a median survival rate of 9-10 months. In fact, HER-2+ BC has a higher risk of BM, with a prevalence of 30-53 % and a median survival time of 11-18 months (22). Another study revealed that BM will happen to approximately 50 % of patients with HER-2+. The factors that may explain this is that anti-HER-2 therapy extends the survival of the patients, which in turn brings about brain metastases. Also, trastuzumab, one of the anti-HET-2 therapies, has only limited permeability to the blood-brain barrier (BBB), which makes the brain a "sanctuary" site for metastases (23).

Simsek et al. (2022) stated that the development of BM occurs in a shorter period in BC HER-2+, compared to the HER-2-, with a median duration of 20.4 months *vs*. 37.7 months, respectively (p=0.018) (24). The patient developed BM within 20 months after the time of diagnosis. The possible underlying mechanisms of BM in HER-2 negative BC are that there are several more signaling pathways involved in metastatic breast cancer, such as Wnt and Notch, PI3K/AKT/ mammalian target of rapamycin (mTOR) and PTEN, and ERBB pathway (23). In addition, the median survival of brain metastases in BC HER-2+ was also shorter than that in the HER-2- group (5.3 *vs*. 11.1 months, p = 0.014). Furthermore, a more recent study disclosed a newly identified HER-2 classification named HER-2 low subtype of breast cancer with different clinicopathological characteristics and outcomes compared to HER-2 positive and HER-2 negative BC (25).

In advanced MBC with metastases, a combination of endocrine therapy and targeted agents is recommended, as is the case for FBC. First-line systemic therapy for hormone receptor+, HER-2-, and unresectable BC with metastases is an aromatase inhibitor in combination with a CDK4/6 inhibitor or ribociclib or abemaciclib, or palbociclip. Another first-line regimen consists of fulvestrant combined with a CDK4/6 inhibitor or palbociclib or abemaciclib, or palbociclib. More recommended agents include the anthracycline groups (doxorubicin, liposomal doxorubicin), the taxanes group (paclitaxel), the anti-metabolites group (capecitabine, gemcitabine), and microtubule inhibitors (vinorelbine, eribulin) (18). A series of phase II clinical trials revealed promising results in chemotherapy-naïve and heavily pre-treated MBC receiving the combination of intravenous vinorelbine and capecitabine (26). Our patient received Vinorelbin-Capecitabine. Capecitabine is listed in the guidelines for treating BC with brain metastases, while vinorelbine is a microtubule inhibitor also recommended as systemic therapy in BC with metastases (26). That combination was not stated in the guidelines. In this case, the combination of capecitabine-vinorelbine was used due to the limited resources.

Overall, the three highest causes of death in MBC are breast cancer itself, cardiovascular disease, and other cancers. Cardiovascular disease is the main non-cancerous cause and is more frequent in older patients. This could be due to cardiotoxicity from chemotherapy and high rates of cardiovascular disease as a comorbidity (27). Andrykowski et al. state that male patients with a history of cancer have higher rates of obesity, diabetes mellitus, and limitation of physical activity due to limited physical, mental, and emotional abilities (28). 97.4 % of patients with MBC received tamoxifen therapy with a thromboembolic effect. Chemotherapy also increases the risk of cardiovascular system dysfunction. Cardiovascular events emerge following the administration of Vinorelbine-Capecitabine. Other adverse effects may be low hematological toxicity, diarrhea, stomatitis, and hand-foot syndrome. Infection was found to be one of the causes of death, but the incidence was not significant. Other causes are problems with the respiratory, endocrine, nervous system, genitourinary, and digestive systems (29). Our patient had a history of uncontrolled diabetes mellitus. He had been hospitalized for more than 30 days, along with septic shock, bacterial pneumoniae, anemia, and electrolyte imbalance. He died on day 5 of hospitalization presumably due to sepsis caused by recurrent pneumoniae. Given his underlying condition—uncontrolled

diabetes mellitus and prolonged length of stay at the hospital, he might be prone to hospital-acquired infection, which led to a poorer prognosis. However, other adverse effects could also add to the risk.

CONCLUSION

We report a male patient with HER-2 negative invasive ductal breast carcinoma in Indonesia. He underwent mastectomy, endocrine therapy, and adjuvant chemotherapy. He once started becoming unable to control the movement of his left extremities. Further examinations revealed brain metastases. BMBC is more common in HER-2+ types. The atypical manifestation in this case might be due to other possible metastatic pathways. The patient died from cardiovascular events on day 5 of the chemotherapy.

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