False Negative Tests in Breast Cancer: A Case Report

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Abstract:

Background: Breast cancer is the most common cancer worldwide. An early and accurate diagnosis is essential in optimizing the disease outcome. Triple assessment, which includes clinical assessment, imaging and pathological examination, is recommended for diagnosing breast cancer.

Case: A 43-year-old lady with a strong family history of cancer presented with a right breast lump for 2 months. Physical examination revealed a 2x3 cm mass in the right breast with no malignancy features. Mammogram and ultrasound revealed BI-RADS 1 (negative) and BI-RADS 2 (benign) respectively. A lumpectomy was done, and the sample was sent for pathological examination. The result came back as a grade 2 invasive breast carcinoma, no special type, stage pT1b. ER was negative while PR and HER2 were not tested. The patient then underwent a right total mastectomy with level II axillary clearance. CT thorax, abdomen & pelvis was scheduled a month later to complete the cancer staging. PR and HER2 status were tested for further management.

Conclusions: All 3 components of triple assessment are indispensable for diagnosing breast cancer. Despite the high sensitivity of imaging modalities, the minimally invasive biopsy technique (MIBT) is still the gold standard. False-negative tests can happen due to multiple factors; they should not become the absolute guidance for further management of patients. A doctor's clinical judgment, based on thorough history taking and physical examination, is more important in guiding the next step of patient care.

Keywords: Breast Neoplasms, Mammography, Ultrasonography, Biopsy

Introduction

Cancer is a leading cause of death worldwide, with nearly 10 million or 1 in 6 deaths in 2020 (1). Among all cancer types, breast cancer stands at the top, with 2.3 million (11.7% of all cancer cases) and 685 000 deaths in 2020. Women have more disability-adjusted life years (DALYs) lost from breast cancer than any other cancer (2). Incidence rates in transitioned countries are 88% higher than in transitioning countries, but mortality rates are 17% lower. This could be due to a higher detection rate through mammographic screening, higher prevalence of modifiable risk factors (Table 1), (2-4) and distribution of Ashkenazi Jewish women in Israel and Europe, who have an exceptionally high risk of BRCA1/2 gene mutation which leads to breast cancer (4). Unfortunately, half of breast cancer incidents occur in women without identifiable risk factors except being female and age over 40 years old. Furthermore, even with all modifiable risk factors controlled, there is only a maximum 30% decrease in the risk of developing breast cancer (2). Therefore, early diagnosis of breast cancer is imperative in optimizing the disease outcome, when less complex interventions with lower costs are required (3).

Mammography is an X-ray imaging modality commonly used in breast cancer screening and diagnosis (5). It has sensitivity at 63-95% and is the only test proven to reduce mortality in screening asymptomatic populations (6). In symptomatic patients, diagnosis is based on triple assessment, i.e., a combination of clinical examination, imaging and pathological assessment (7). Clinical examination includes a thorough history taking for risk assessment and clinical breast examination. General symptoms of breast cancer include palpable mass, breast pain and nipple discharge. Hard and fixed mass, asymmetric thickening or nodularity, overlying skin changes (peau d'orange, erythema, nipple excoriation, scaling or eczema, skin ulcer, satellite skin nodule), blood-stained nipple discharge and axillary mass are features suggestive of malignancy. For women >35 years, combined reporting of mammography and ultrasound (CRMU) is recommended (3). For women <35 years, ultrasound is preferred as the sensitivity of mammography reduces significantly in dense breasts (8). MRI and newer techniques like digital breast tomosynthesis (DBT), 3D ultrasound, shear wave elastography and contrast-enhanced mammography are not routinely performed (7). A standardized report system, known

as Breast Imaging Reporting and Data System (BI-RADS) is then used to report the findings and evaluate its benignity or malignancy (5). The last component of the assessment is a pathological examination of the primary tumor, as well as suspicious axillary nodes (7). Minimally invasive biopsy techniques (MIBT) such as core needle biopsy and fine-needle aspiration cytology (FNAC) are preferably done with ultrasound guidance to increase sampling accuracy and optimize patient comfort. Core needle biopsy provides better characterization of tumor type, marker analysis and immunohistochemistry (3). An excisional biopsy is not recommended unless repeated negative core biopsies (7). Final diagnosis should be made based on the 2019 World Health Organization (WHO) classification of breast tumors and the 8th edition of the American Joint Committee on Cancer (AJCC) tumor, node, metastasis (TNM) staging system (3,7).

Table 1. Modifiable and non-modifiable risk factors of breast cancer

Non-modifiable	Modifiable
Age: Risk increases with age, peaking at 60-64 years.	**Reproductive factors:** Nulliparity, lack of breastfeeding, older age at first live childbirth
Gender: Risk of female>male	**Hormonal factors:** Oral contraceptives (OC) use (current use, use ≥10 years, <10 years since last use), progestogen OC use ≥5 years, combination hormone replacement therapy, long term unopposed estrogen use (>15 years)
Family history: Family history of breast cancer at a young age, carrier of pathogenic variants (BRCA1/2, PALB2, ATM, CHEK2)	**Hormonal factors:** Oral contraceptives (OC) use (current use, use ≥10 years, <10 years since last use), progestogen OC use ≥5 years, combination hormone replacement therapy, long term unopposed estrogen use (>15 years)
Reproductive factors: Early menarche (≤12 years old) and late menopause (≥50 years old)	**Lifestyle:** Overweight/ obese, lack of physical activity, alcohol >10g/day, exposure to tobacco smoke
History of neoplastic disease of the breast **Breast density:** 2x risk in scattered fibro glandular density (BI-RADS-B), 4x risk in extremely dense breast (BI-RADS-D)	**Radiation exposure:** irradiation to the chest

The Case

A 43-year-old lady with no known medical illness presented with a right breast lump for 2 months. It is occasionally painful on touching, described as prickling pain with a pain score of 1-2. Otherwise, it does not increase in size, no overlying skin changes, and no nipple discharge or retraction. She had a weight loss of 18kg (83kg to 65kg) within 2 years, claimed due to strict diet control and regular exercise. She had no loss of appetite, no lethargy and no metastatic symptoms such as dyspnea, bone pain, jaundice or neurological symptoms. She had early menarche at 12 years old and her first childbirth at 31 years old. She breastfed her 2 children for 6 months, and never used oral contraceptives or received any hormone replacement therapy. However, she had a strong family history of cancer. Her maternal aunt was diagnosed with breast cancer at 50 years of age, surgery and chemotherapy were done but there was recurrence 10 years later, and she subsequently passed away within a month. Her late maternal grandfather and grandmother were diagnosed with colon and liver cancer respectively at 60+ years, and were on palliative care with no surgery done. She did not smoke, and she drank alcohol occasionally.

On physical examination, bilateral breasts are symmetrical, and overlying skin and nipples appear normal. There was a 2x3cm mass in the right breast at 9 o'clock direction, 2cm away from the nipple. The mass is soft and non-tender, and the surface is smooth with a well-defined edge. It is not warm, non-mobile, non-fluctuant, not tethered to the skin and not fixated to the pectoralis muscle. There was no palpable axillary, supraclavicular or cervical lymph node. Systemic examinations were normal. The patient then underwent both a mammogram and ultrasound, which showed different findings. The mammogram revealed normal fibro glandular tissues with no mass or lesion seen, no suspicious-looking calcification, and no axillary nodes seen, hence concluded as BI-RADS 1 (negative/ normal study). Ultrasound showed the presence of a 17x12mm thin-wall, well-defined, homogeneously anechoic cyst at the 9 o'clock position in the right breast. Otherwise, no other lesions and no axillary nodes were seen. Ultrasound gave an impression of BI-RADS 2 (benign). A lumpectomy was done and the breast tissue was sent for histopathology and immunohistochemistry examinations. Surprisingly, the result came back as a grade 2 invasive breast carcinoma, no special type,

staged at pT1b and malignant cells was seen at the excised margins. Estrogen Receptor (ER) was negative, Progesterone Receptor (PR) and Human Epidermal Growth Factor Receptor 2 (HER2) were not examined. The patient then underwent a right total mastectomy (Figure 1) with level II axillary clearance (Figure 2). The operation was uneventful and there were no complications such as seroma formation, lymphoedema, wound infection, hematoma and skin flap necrosis. The first drain was off on day 3 post-op and the second drain off on day 8 just before discharge. CT thorax, abdomen & pelvis was scheduled 1 month later to complete the staging. On day 10 post-op, the clinic's follow-up revealed good wound healing and the suture was off. Further management would be planned after confirming the staging by CT as well as PR and HER2 status.

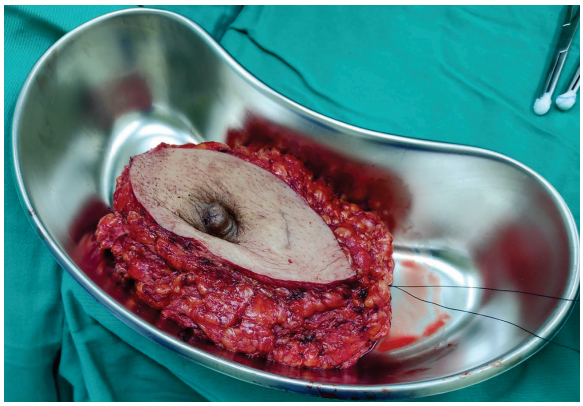

Figure 1 Total right mastectomy.

Long suture (red arrow) indicates lateral pole, short suture (green arrow) indicates superior pole. There is a 2 cm vertical flat lumpectomy scar in 9 o'clock direction, 3cm away from the nipple (yellow arrow).

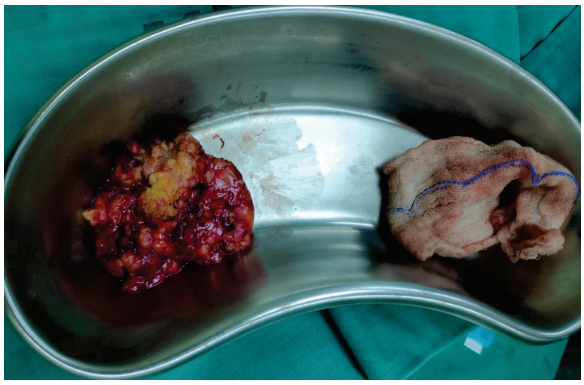

Figure 2 Level II Axillary Clearance.

Discussion

Combined reporting of mammography and ultrasound (CRMU) is recommended for patients with palpable breast masses (3). Mammogram and ultrasound have a sensitivity of 87.8% and 80.1% respectively (10). The addition of ultrasound to mammography reduces the false-negative rate from 15% to 2.4%, according to Chan and colleagues. They also predicted that the cancer rate and negative predictive value of a palpable breast mass of BI-RADS 1–2 to be 0.3% and 99.7% respectively (9). Nevertheless, a diagnosis of breast cancer could still be missed which leads to a delay in treatment, a higher risk of systemic

dissemination and hence a worse prognosis. Febles classified the possible causes into 6 main groups which are breast radiological anatomy, lesion radiological characteristics, radiologist performance, equipment quality, radiographer performance and imaging environment. Measures such as imaging quality control, professional training, repeated image reading and computer-aided detection could be done to diminish false-negative occurrences (8).

In this case, the patient is at high risk of breast cancer due to her age, strong family history of cancer and early menarche (longer duration of estrogen exposure). However, clinical breast examination gave an impression of a benign cyst, then further augmented by mammography and ultrasound findings: BI-RADS 1 and BI-RADS 2 respectively, which are suggestive of a 0% chance of malignancy. However, the histopathological result came back as a Grade 2 invasive breast carcinoma, no special type at pT1b stage. Initially, a lumpectomy, instead of a core needle biopsy or FNAC was done due to the diagnosis of a benign cyst. Fortunately, the excised tissue was sent for pathological examinations which overturned the previous impression and confirmed a final diagnosis of breast cancer.

The immunohistochemistry testing is incomplete; ER was negative, and PR and HER2 were not tested, thus unable to continue further workup on the treatment plan. Both hormone receptors (ER & PR) and HER2/ c-erb B2 status should be assessed for all samples of suspected breast cancer (3).

Conclusions

Triple assessment, which includes clinical assessment, imaging and pathological examination, is necessary for diagnosing breast cancer. Despite the high sensitivity of imaging modalities, minimally invasive biopsy technique (MIBT) such as core biopsy and fine-needle aspiration cytology (FNAC) is still the gold standard. False-negative tests can happen due to multiple factors; they should not become the absolute guidance for further management of patients. A doctor's clinical judgment, based on thorough history taking and physical examination, is more important in guiding the next step of patient care.

Declarations

Ethics approval and consent to participate

Informed consent of publication was obtained from the patient.

Availability of data and material

Not applicable.

Conflict of interests

The author has no conflicts of interest to disclose.

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Authors' contributions

YX Lee was the sole contributor of the manuscript

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