

Triple Positive breast cancer: A case series

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Established Facts and Novel Insights

Established Facts:

- The molecular tumor profiling has enabled detailed classification based on gene expression, each category with a distinct management.
- Molecular subtypes include: Luminal A (hormone receptor positive, HER2-, lower proliferating index), Luminal B (lower level of positive estrogen or progesterone receptor negative, sometime with HER2+, higher proliferating index), HER2+, basal-like subtype (usually triple negative) and claudin-low subtype, less reproducible defined yet (usually triple negative BC)

Novel Insights

- Existence of rare cases as ‘Triple Positive’ invasive ductal carcinoma of breast with hormone receptor and HER2 positive status
- Novel insight into the treatment option for ‘Triple Positive’ breast cancer

Abstract

Introduction: Breast cancer is the most common malignancy in women around the world, accounting for 25.1 % of all cancers among women. Breast cancer are classified in different molecular subtypes depending on hormone receptor positive or negative and human epidermal growth factor receptor 2 status. All the three receptors labelled as ‘triple positive’ breast cancer are rare entity. We herein describe a case series of three patients diagnosed as invasive ductal carcinoma with Immunohistochemistry (IHC) positive for all three receptors (Hormone receptors and human epidermal growth factor receptor).

Case presentation: Three patients aged 67, 40 and 34 years presented with breast lump and were diagnosed invasive ductal carcinoma. There was no history of familial breast cancer, any other malignancy, or hormonal medication. Modified radical mastectomy was done and specimen sent to surgical pathology department for histopathology. Modified Bloom Richardson’s score was 7 and 8 with histological grade 2 for two of the cases. IHC was performed and was positive for Hormone receptor and human epidermal growth factor receptor. All the three cases were labelled as ‘Triple Positive’.

Conclusion: Breast cancer with all three receptor positive are rare to find but these cases do exist. The biological significance and cross talks of their related pathways should be investigated further for ‘triple positive’ breast cancer to determine intrinsic as this would help to view the treatment options if these patients receive endocrine treatment in combination with HER2 blocking agents or a separate therapy.

Key words: Breast cancer; Hormone receptors; Triple positive

Introduction

Breast cancer is the most common malignancy in women around the world, accounting for 25.1 % of all cancers among women.[1]

The molecular tumor profiling has enabled detailed classification based on gene expression, each category with a distinct management. There are five subtypes of breast cancer in molecular classification: Luminal A (hormone receptor positive, HER2-, lower proliferating index), Luminal B (lower level of positive estrogen or progesterone receptor negative, sometime with HER2+, higher proliferating index), HER2+, basal-like subtype (usually triple negative) and claudin-low subtype, less reproducible defined yet (usually triple negative BC).[2,5]

The standard treatment of Breast cancer differs in between the molecular subtypes. Luminal A and B subtype treatment is primarily by hormone-based therapy, that of Triple negative/Basal like is based on chemotherapy and that of HER2+ve is monoclonal antibody.

However, cases with all three receptor positive ‘Triple Positive’ are rare. We describe here a series of three cases, diagnosed as Invasive ductal carcinoma, that were hormone receptor and Human epidermal receptor 2 (HER2) receptor positive.

Case 1: A 67 years old female patient presented with complaints of a painless mass in right breast since 9 months. Physical examination of the patient illustrated a hard and well-defined mass

measuring 5 × 4 cm, in the upper inner quadrant of right breast, nipple and areola was fixed to the underlying skin. There was presence of puckering and peau-d'orange appearance. Significant lymphadenopathy was present in the right axillary region. There was no history of familial breast cancer, any other malignancy, or hormonal medication. On USG breast, findings were suggestive of carcinoma right breast with right axillary metastatic lymphadenopathy. The patient underwent biopsy followed by right Modified radical mastectomy with axillary lymph node dissection.

Gross examination of specimen revealed tumor size of 5 × 4 × 2.5 cm. A total 15 axillary lymph nodes were identified. Histology diagnosis was Invasive ductal carcinoma of breast. Modified Bloom Richardson Score was calculated to be 7, with histopathology grade II. Two out of 15 lymph nodes were positive for metastatic deposits of infiltrating ductal carcinoma. Immunohistochemistry was done for hormone receptor status on the tumor sections and demonstrated; intensity score 03 and proportion score 03 with total Allred score 06 for ER; intensity score 03 and proportion score 03 with a total Allred score of 06 and PR, i.e., strongly positive. HER2/neu staining demonstrated complete, uniform, intense membrane staining in more than 30% of invasive tumor cells and was scored 3+ i.e., strongly positive. (Figure 1.)

Case2: A 40 years old female patient presented with complaints of a painless lump in her right breast since 1 month. The lump was insidious in onset; gradually progressive, initially small and gradually increased to the size of 2 x 2 cm. Physical examination of the patient illustrated a hard and well-defined mass measuring 2 × 2 cm, in the upper outer quadrant of left breast. The lump was ill defined, with speculated margins. Overlying skin was normal with no nipple discharge, no peau-d'orange and no puckering was seen. Single lymph node was present in left axilla, firm in consistency, non-tender. There was no history of familial breast cancer, any other malignancy, or hormonal medication.

On USG: Left breast shows hypoechoic mass of 30 x 20 mm in upper outer quadrant with speculated margins and calcification. Left axilla shows one lymph node of size 16 x 8 mm with eccentric cortical puckering of 6.3 mm, another small lymph node of size 11 x 5 mm which was reactive lymph node. The USG findings was suggestive of carcinoma left breast with metastatic lymphadenopathy. Fine needle aspiration Cytology (FNAC) was done and the cytology findings suggested Ductal carcinoma. The patient underwent left Modified radical mastectomy with axillary lymph node dissection.

Gross examination of specimen revealed tumor size of 3.0 × 2.5 × 1 cm and total 10 axillary lymph node were identified. Histology diagnosed it as Infiltrating ductal carcinoma of left breast, Modified Bloom-Richardson BR Score was 8 and histology grade III. All lymph node were negative for metastatic deposits on histopathology.

Immunohistochemistry was done for hormone receptor status on the tumor sections and demonstrated; intensity score 02 and proportion score 02 with total Allred score 04 for ER; intensity score 02 and proportion score 02 with a total Allred score of 04 for PR, i.e., positive.

HER2/neu staining demonstrated complete, uniform, intense membrane staining in more than 30% of invasive tumor cells and was scored 3+ i.e., strongly positive. (Figure 2)

Case 3: A 34 years old female patient presented with complaints of a painless lump in her left breast since nine months. Physical examination of the patient illustrated a lump of size 8 x 6 cm involving all four quadrants of left breast. It was hard in consistency, fixed to underlying skin and non-tender. Puckering and dimpling present along with Peau-d'orange present. Lump was not fixed to the underlying muscle. No pus or discharge was present from the nipple. Multiple axillary lymph nodes were palpable in left axilla. Contralateral right breast was normal on examination but single lymph node was palpable in right axilla.

USG was done and findings suggested carcinoma of left breast with metastatic lymphadenopathy. FNAC and trucut biopsy was sent for histology examination.

Grossly multiple, whitish, thread like tissue pieces aggregating 2 x 0.5 cm were received as trucut biopsy specimen. Section stained with hematoxylin and eosin examined for histology suggested a diagnosis of Infiltrating ductal carcinoma (Mucinous type).

Immunohistochemistry was done for hormone receptor status on the on biopsy block and demonstrated; intensity score 03 and proportion score 02 with total score 05 for ER; intensity score 02 and proportion score 01 with a total score of 03 and PR, i.e., strongly positive. HER2/neu staining demonstrated complete, uniform, intense membrane staining in more than 30% of invasive tumor cells and was scored 3+ i.e., strongly positive.

Discussion

The term “triple-positive” breast cancer was first introduced by Vici et al. to describe a distinctive subtype.[6] It is defined as a luminal HER2 tumor which expresses both the ER and PR. This type of tumor also expresses high HER2 levels and exhibits a biologically distinct phenotype and specific clinical behavior. In current clinical settings, systemic therapeutic approaches for triple-positive breast cancer comprise hormone receptor (HR)-specific hormonal therapies, HER2-directed therapy, and systemic chemotherapy.

Breast cancer involves multiple abnormal regulation pathways, dominated by estrogen receptor (ER) and human epidermal growth factor receptor 2 (HER2) signaling pathways. Current research identified the presence of numerous cross talks between the two capital pathways, enabling cancer cells to become resistant to chemotherapy or hormone therapy; blocking one pathway augments and up-regulates other alternate pathways.[7,8] “Triple positive” breast cancer subtype consisting of high levels of HER2, estrogen and progesterone receptors expression seems promising in better understanding and treating BC patients.

Assessment of this new distinct subtype of triple positive breast cancer with HR+ and HER2+ raises a series of problem concerning its treatment. It is also believed that HER2 blocking agents are effective in patients with HER-2-positive disease, irrespective of HR status.[9] In one of the study HER2+ breast cancer tumors with HR+ were divided in subgroups and analyzed; differences in behavior and response to treatment were observed when high levels of HR were found compared to low HR expression in patients with HER2-enriched breast

cancer. The concept of “triple positive” breast cancer, defined by high level expressing HR of HER2 positive breast cancer, emerged, with distinct response to conventional treatment. A subset of small HER2+, ER/PR positive (“triple positive”), breast cancer might be focused primarily by HR status, and biologically behave more likely HER2 negative, HR positive breast cancers. However, question remains if these patients receive endocrine treatment in combination with HER2 blocking agents, without chemotherapy or the administration of anti-HER2 agent always necessary.

Molecular classification plays an increasingly essential role in the personalized care of breast cancer, and the three key molecular determinants, HER2, ER and PR, are evaluated in routine clinical practice. The biological significance and cross talks of their related pathways should be investigated further to determine intrinsic heterogeneity of breast cancer and inform treatment decisions in the complexities of the clinical setting, with the identification of further tumor subtypes amenable to targeted and innovative treatments representing a research priority.

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Statement of Ethics: Informed consent was obtained from the patient and the study protocol and permission to conduct the study and publication was obtained from Institutional Ethic Committee.

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Authors Contributions

Vivek Gupta (VG) and Prerna Agarwal (PA), Sunita Vagha (SV) carried out the study, contributed to concept and design of study. VG did reporting of case, acquisition of data along with analysis and interpretation. VG drafted the manuscript and reviewed it and also gave final approval for submitting and publication. VG and PA helped in drafting and revised the manuscript and also gave approval for the submitting and publication. Rashmi Wankhade (RA) helped in drafting the manuscript and gave approval for submitting and publication

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Figure1: Photomicrograph of case1 Invasive ductal carcinoma. a: HE staining x 100. b: estrogen receptor (ER) positive. c: progesterone receptor (PR) positive. d: HER2 positive. Immunohistochemistry staining, x 100.

Figure2: Photomicrograph of case2 Invasive ductal carcinoma. a: HE staining x 100. b: estrogen receptor (ER) positive. c: progesterone receptor (PR) positive. d: HER2 positive. Immunohistochemistry staining, x 100.

Figure3: Photomicrograph of case3 Invasive ductal carcinoma. a: HE staining x 100. b: estrogen receptor (ER) positive. c: progesterone receptor (PR) positive. d: HER2 positive. Immunohistochemistry staining, x 100.

Figure1: Case1 Invasive ductal carcinoma. a: HE staining x 100.
b: estrogen receptor (ER) positive. c: progesterone receptor (PR) positive. d: HER2 positive. Immunohistochemistry staining, x 100.

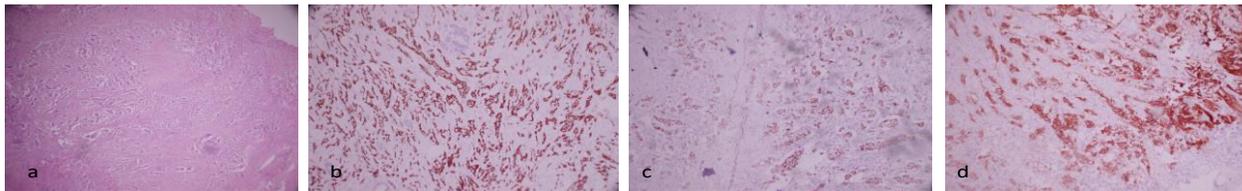


Figure3: Case3 Invasive ductal carcinoma. a: HE staining x 100. b: estrogen receptor (ER) positive. c: progesterone receptor (PR) positive. d: HER2 positive. Immunohistochemistry staining, x 100.

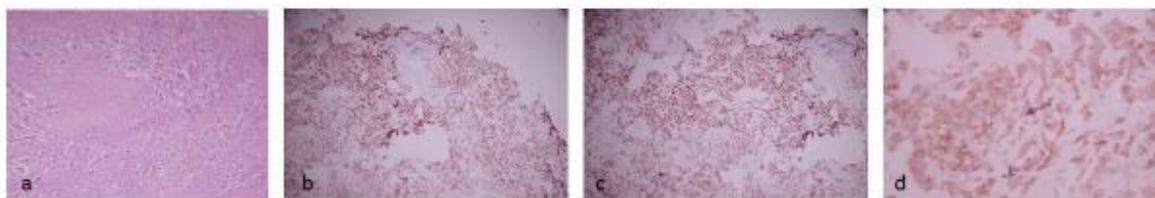


Figure2: Case2 Invasive ductal carcinoma. a: HE staining x 100. b: estrogen receptor (ER) positive. c: progesterone receptor (PR) positive. d: HER2 positive. Immunohistochemistry staining, x 100.

