HLA A24 Associated Tumor Immunity in HER2/neu Positive Breast Cancer

Ravi Pratap Singh¹, Chintamani², AK Mandal³

Abstract

Breast carcinoma is the most common tumor in women and it has resulted in significant morbidity and mortality. Recognition of tumor-associated antigens (TAA) by HLA class I-restricted CD8+ T cell is fundamental for the detection and destruction of malignant cells. HLA A24 has been shown to be associated with presenting peptides in breast carcinoma, which can be targeted for cancer immunotherapy. Overexpression of the HER2 receptor tyrosine kinase is associated with more advanced-stage disease at presentation and a rapidly progressive clinical course. Here we present a case of a 57-year-old female, who presented with a left breast lump. On histopathological examination, diagnosis of infiltrating ductal carcinoma was made. The patient had ER, PR negative and HER/neu positive cancer with nodal metastasis to supraclavicular lymph nodes. Course of Antracycline-based chemotherapy was started. Patient showed no signs of recurrence till the time of writing the article.

Keywords: HLA A24, Breast cancer, HER2/neu, Infiltrating ductal carcinoma

Introduction

According to National Cancer Registry Programme 2012-2014, breast cancer is the most common cancer in women in India. Conventional treatment approaches for advanced breast cancers are highly invasive.¹ HLA A is a part of gene complex of HLA on 6p21. These genes encode major histocompatibility proteins. These cell surface proteins are responsible for the regulation of the immune system. These proteins present small peptides to cells of immune system.

Presence of homozygous HLA A24 has been reported to be associated to HER2/neu positivity.² HER2/neu-derived peptides induced peptide-specific and tumor-reactive Cytotoxic T lymphocyte activity in the peripheral blood mononuclear cells of HLA-A24(+) breast cancer, but did not induce any such activity in any HLA-A24(−) patients.³ We report a case of HLA A3/A24 haplotype in a Her2-neu enriched carcinoma breast.

Case Report

A 57-year-old lady having a 3.2×2.5 cm left breast mass along with enlarged left and supraclavicular lymph nodes was diagnosed with infiltrating ductal carcinoma of left breast. Patient had no distant metastasis on radiological examination. Clinically, the patient was graded T3N1M0. She underwent left modified radical mastectomy.

¹²³Vardhman Mahavir Medical College and Safdarjung Hospital, New Delhi – 110029, India.

Correspondence: Dr. Ravi Pratap Singh, Vardhman Mahavir Medical College and Safdarjung Hospital, New Delhi – 110029.

E-mail Id: ravipsingh99@gmail.com

Orcid Id: http://orcid.org/0000-0001-5133-1326

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On histopathological examination of the mastectomy, the patient was graded pT3N2a, Stage II with infiltrating ductal carcinoma. The receptor status was ER- and PR-negative and Her2/neu positive. And the surrogate molecular classification was Her2-neu enriched. The patient has completed four cycles of anthracycline-based chemotherapy and was started on Trastuzumab and concurrent radiotherapy at the time of writing.

Normal saline-preserved tumor tissue was obtained from the modified radical mastectomy specimen. To extract the DNA, the tumor tissue was finely ground in aseptic conditions and was kept for digestion for 4 hours with digestion buffer and proteinase K provided with Purelink® genomic DNA kit, at 55°C. RNase was added to the digested lysate. Lysate was centrifuged at 12000 rpm for 3 minutes. After centrifugation, the supernatant containing DNA was obtained. Purified DNA was extracted using a Purelink® genomic DNA kit. The concentration and presence of DNA was confirmed by spectrophotometry. The obtained DNA was amplified using polymerase chain reaction which took place in the microtiter plate provided with the Purelink® genomic DNA kit. The data was read by FluoVista analyzer, which is based on specially modified TaqMan® probe system, prior to and after PCR and results were analyzed by using fluorgenic software. This patient showed the presence of HLA A3/A24 alleles.

Discussion

Loss or altered class I HLA antigen expressions in tumor cells is believed to lead to defect in recognition of tumor antigens by CD8+ T lymphocytes. Failure of recognition of tumor cells leads to their escape from immune attack and poses problems in the design of antitumor immunotherapy. It was found that down-regulation of HLA class I expression in breast cancer was significantly associated with the stage of tumor, metastasis to nodes and lymphovascular invasion. HLA class I positive patients had significantly longer disease-free survival (DFS) than those without HLA class I positivity. Madjid et al. investigated HLA class I expression in breast cancer and showed that patients with a negative HLA class I phenotype had a better postoperative outcome.

The chances of a cell becoming malignant depend not only on the level of tumor expression of MHC class I but also on the molecular mechanisms, which cause alterations in the MHC class I expression. Generation of various tumor MHC phenotypes can occur at any step required for the protein synthesis, assembly, transport or expression on cell surface.

Recognition of tumor-associated antigens (TAA) by HLA class I-restricted CD8+ T cells is fundamental for the detection and destruction of malignant cells (van der Bruggen et al. 1991). Although new protocols have shown increased number of T lymphocytes associated with tumor immunity, clinical benefits have been limited. (Rosenberg et al. 2004). Morabito et al. (2009) observed that down-regulation of HLA class I expression in breast cancer had significant association with adverse prognostic factors. Kaneko et al. observed that patients with intact HLA class I had a better disease-free interval when compared to those with loss of HLA class I.

Despite the recent advances in the understanding of role of HLA class I antigen expression in tumors, information regarding its prognostic value or its association with patient outcome is still controversial and not fully understood. It can be explained due to high degree of polymorphisms in HLA gene frequencies found in different population.

HER2 is a type 1 transmembrane protein receptor tyrosine kinase. Its overexpression leads to interaction with any available receptor tyrosine kinase binding partner, even in the absence of ligand (Elster et al., 2015). A cascade of flow of downstream signals ensues in pathways such as the phosphoinositide-3-kinase pathway, which promotes cell growth, proliferation, and metastasis (Subbiah and Gonzalez Angulo, 2014).

HER-2/neu is expressed in early disease in a large percentage of ductal carcinoma in situ (DCIS) lesions. HER-2/neu expression is associated with an increased risk of invasion and recurrence and an additional risk of developing resistance to immunotherapy in patients with extensive disease. Loss of anti-HER-2 Th1 response is specific, not readily reversed by standard therapies, correlates with lack of complete response to neoadjuvant therapy and diminished disease-free survival. This defect can be restored with HER-2 vaccinations in both DCIS and invasive breast cancer.

Overexpression of the HER2 receptor tyrosine kinase is associated with more advanced-stage disease at presentation and a rapidly progressive clinical course, including enhanced local-regional extent, early metastatic spread, and resistance to chemotherapy (Pohlmann et al., 2009), which translates to poor clinical outcomes.
Both humoral and cellular responses have been demonstrated in breast cancer. A large retrospective case-control study linked high levels of autoantibodies against HER2 and decreased risk of developing both DCIS and invasive breast cancer (Tabuchi et al. 2016). Analysis of whole transcriptome of a HER2-positive breast cancer cohort demonstrated a strong association between immune gene expression and recurrence-free survival following the treatment with adjuvant Trastuzumab (Perez et al., 2015). This study demonstrated an inverse correlation between HER2-overexpression results in MHC Class I down regulation by involving the RAS/MAPK pathway. These findings suggested a role for RAS/MAPK pathway inhibitors in improving MHC Class I expression in breast cancer cells.

In a Malaysian study, HLA A24 expression was negatively associated with lymph node metastasis. Her-2/neu expression was positively correlated to homozygous HLA A24 and negative to HLA A11/24 haplotype.

Mammaglobin-A (Mam-A) is a breast cancer-associated protein which is expressed in up to 80% of human breast cancers. Because of near-ubiquitous expression by all kinds of breast cancers, Mam-A offers a superior antitumor breast cancer target over other TAA-like MUC1 and Her-2/neu which are expressed only in 20–30% of breast cancers. HLA-A24-restricted Mam-A-derived CD8+ CTL epitopes have been identified and it has been demonstrated that it is possible to develop Mam-A-reactive CD8+ CTL lines in vitro that recognize breast cancer cells naturally expressing Mam-A-derived peptides.

HER2/neu derived immunogenic cytotoxic T lymphocyte (CTL) epitope peptides capable of inducing both cellular and humoral responses in HLA A24 positive breast cancer patients have been identified. Thus, HLA A24 has been shown to be associated with presenting peptides in breast carcinoma, which can be targeted for cancer immunotherapy. Presence of homozygous HLA A24 has been reported to be associated with HER2/neu positivity. However, HER2/neu positivity is strongly associated with increased disease recurrence and a poor prognosis.

To conclude, role of HLA genes is complicated in tumor immunity and loss of their expression at any stage is associated with poor clinical outcome since the tumor proliferates unchecked by immune system. HER2 expression in this patient allows for initiating targeted immunotherapy with Trastuzumab, but the negative ER and PR receptor status suggests an adverse clinical outcome and high chances of relapse. There is paucity of literature on HLA A24 and its correlation with breast cancer. Identification and elaboration of normal and pathological function of HLA A24 and HER2 will help fill the lacunae in the existing knowledge of breast cancers. A need for studies including a larger cohort of patient is required to further establish the findings which will help guide the development of specific cancer immunotherapies.

Conflict of Interest: None

References

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