Review

Expression of ER, PR, her-2/neu and BRCA-1 in Breast Carcinoma – A Review

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Abstract

The present paper attempts to highlight a rare case of neural arborization in axilla. Anatomical Despite the development of high throughput technologies such as DNA microarrays, it now appears that IHC may play an increasing important role in clinical management of breast cancer. Various tumor markers for breast carcinoma are ER, PR, Her-2/neu, PCNA, Ki67, bcl2, p53, BRCA 1, BRCA 2, cyclin D, cyclin E, p21 protein, p27, Milk globule membrane antigen, Ki67, cathepsin D, E-cadherin, vimentin, beta catenin, carcino embryonic antigen (CEA) Oncotype D_x, B72.3, BCA 225. Hence, the present review discusses literature regarding various tumor markers and evalution of these markers will predict prognosis, disease free survival, genetic inheritance and aid in treatment planning.

Keywords: Biomarkers; Immunohistochemistry; Hormonal therapy; Prognosis; Women nerve; Axilla

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INTRODUCTION

Immunohistochemistry (IHC) is a technique for identifying cellular or tissue constituents by means of antigen antibody interactions, and is used to detect various tissue antigens causing cancer and are helpful in predicting the prognosis and treatment. IHC was first used for detection of nuclear retinoblastoma gene (RB) expression in formalin paraffin sections of human cancer because of convenience, economy and compatibility with routine surgical pathology practice.Tumor biology allows for a number of potential intracellular targets. Many tumors are hormone dependent. The presence of hormone receptors can be used to determine if a tumor is potentially responsive to antihormonal therapy. One of the first therapies was the antiestrogen - tamoxifen, used to treat breast cancer. Such hormone receptors can be detected by immunohistochemistry.[1] Recent progress in IHC and molecular biology techniques has enabled in depth investigation of molecular biology of breast tumors associated with BRCA1 and BRCA 2 genes. BRCA1 associated tumors appear to show an increased frequency of TP53 mutations, frequent p53 protein stabilization and absence of immunoreactivity for steroid hormone receptors. Despite the development of high throughput technologies such as DNA microarrays, it now appears that IHC may play an increasing important role in clinical management of breast cancer.[2]Breast is a modified apocrine sweat gland

that develops into a complex functional structure in females and remains rudimentary in males. Steroid hormones, estrogen and progesterone play an important role in breast development. Estrogen produces duct growth in breast and is largely responsible for breast enlargement at puberty in girls. Progesterone stimulates the development of lobules and alveoli. It induces the differentiation of estrogen prepared ductal tissue and supports the secretory function of breast during lactation.[3] In India, breast carcinoma is the second most common carcinoma with only a narrow figure separating it from the top placed malignancy of cervix, in terms of both incidence as well as mortality.[4] Prognostic factors in breast cancer have exploded over the past several years. The size of the tumor, status of the regional lymph nodes, peritumoral lymphatic involvement, vascular invasion, the receptor status and grade of the tumor are definitely proven important prognostic factors in breast cancer.

CLINICAL PRESENTATION OF BREAST DISEASE:

Breast diseases which may be either benign or malignant may present with various symptoms, of which major are:Pain (mastalgia/mastodynia) is the most common breast symptom,Discrete palpable mass which must be distinguished from normal nodularity of the breast and Nipple discharge which may be physiological or pathological.

Every lump in the breast should be regarded as a possible carcinoma until proved otherwise.[5] Although an accurate history and clinical examination are still the most important methods of detecting breast disease, there are a number of investigations that can assist the diagnosis that includes mammography, ductography, fine needle aspiration cytology (FNAC), Needle Core Biopsy, Histopathological Examination, AgNOR count and Immunohistochemical expression of tumour markers like estrogen and progesterone receptors(ER/PR), Ki67, p53, PCNA, Her-2/neu, cytokeratins, BRCA 1, BRCA 2 etc.[6]Tumor markers are the biochemical indicators of the presence of tumor. They include cell surface antigens, cytoplasmic proteins, enzymes and hormones. Their expression helps in screening, diagnosis, staging, determine prognosis, guide, monitor treatment and determine recurrence. They define a particular disease entity and are targets for therapeutic intervention in clinical trials.[7]Various tumor markers for breast carcinoma are ER, PR, Her-2/neu, PCNA, Ki67, bcl2, p53, BRCA 1, BRCA 2, cyclin D, cyclin E, p21 protein, p27, Milk globule membrane antigen, Ki67, cathepsin D, E- cadherin, vimentin, beta catenin, carcino embryonic antigen (CEA) Oncotype D_x, B72.3, BCA 225.[8]

ESTROGEN RECEPTOR:

An estrogen receptor is a protein molecule found inside those cells that are targets for estrogen action. Estrogen receptors contain a specific site to which only estrogens (or closely related molecules) can bind. The main function of the estrogen receptor is a DNA binding transcription factor transcription factor which regulates gene expression. Estrogen receptor assays predict clinical response correctly in about 2/3 rd of patients with estrogen receptor positive tumors i.e. two third of ER positive tumors respond to hormonal manipulators whereas virtually all (96%) of the ER negative tumors fail to respond to endocrinal therapy.[9] Estrogen receptors expression is found to be around 70% in breast cancer cases studies in west while Indian studies show Estrogen Receptor positivity varying from 24 % to *32.6%.*[9,10,11] ER expression is inversely correlated with tumor grade and low levels are present in familial breast cancers. Estrogen receptor (ER) positive breast cancers generally have a better prognosis and are often responsive to anti-estrogen therapy. Unfortunately ER-negative breast cancers are more aggressive and unresponsive to anti-estrogens.[12]

PROGESTERONE RECEPTOR:

Progesterone receptor (PR) is an intracellular steroid that specifically binds progesterone expressed by a single gene [Chr 11 q 22]. It has two main isoforms A and B that differ in their molecular weight. Estrogen is necessary to induce progesterone receptors. PR along with estrogen receptor (ER) is expressed in various histological types of breast cancer. PR is most frequently present in intraductal, tubular and mucinous carcinoma and infiltrating ductal carcinoma.[13] The incidence of estrogen receptor negative and progesterone receptor positive (ER-/PR+) invasive breast carcinoma is reported to be as high as 21% in India, as compared to 3-5% in the western literature.[14] According to a study conducted by Stierer et al on 299 patients, progesterone receptor status by immunohistochemistry yielded significant correlation with histological grade of malignancy, nuclear polymorphism, rate of mitosis ($p<0.001$) as well as growth pattern ($p<0.01$).[15] According to another study on 1235 cases of breast

cancer, positive receptor remained significant for improved disease free and overall survival in multivariate analysis including the standard variables of tumor size, nodal status, treatment, histological grade, and Her-2/neu status.[16]

HER-2/ NEU:

Her-2/ neu is a protooncogene that is amplified in some of the human breast cancers. It encodes a tyrosine kinase receptor, p185 erb B-2, which is anchored in cell membrane. Activation of this receptor leads to intranuclear activation of c-fos and c-jun.[17] Her-2/neu oncogene over expression is higher (46.37%) among Indian patients in comparison to 20-30% shown in most western literature.[18] The receptor is involved in both differentiation and proliferation. Typically HER-2 amplificated tumors are associated with high grade disease, i.e. high grade often extensive ductal carcinoma in situ and grade 2 and 3 infiltrating ductal carcinomas. Assessment of Her-2/neu is important in targeting therapies for breast cancer notably including Hercepten/Trastuzumab.[17] Her-2/neu gene copy number or expression was found to be associated with reduced disease free and overall survival. It is accepted universally as the new prognostic marker and predictor of therapeutic response in carcinoma breast.[19]

BRCA 1:

BRCA1 is a human caretaker gene that produces a protein called breast cancer type 1 susceptibility protein, responsible for repairing DNA. It is expressed in the cells of breast and other tissue, where it helps repair damaged DNA, or destroy cells if DNA cannot be repaired. If BRCA 1 itself is defective, damaged DNA is not repaired properly and this increases risks for cancers.[20]

Although the majority of BRCA 1 positive cases are sporadic, 5 to 10% of patients are attributed to the inherited mutations in several susceptibility genes that are considered as hereditary. About 40-50% of hereditary breast cancers and the most of the hereditary breast-ovarian syndromes are thought to be due to mutations in BRCA1 gene. Breast cancer susceptibility gene 1 (BRCA1) associated breast cancers often occur in younger women, and such tumors are high grade and lack estrogen receptors. All these features are associated with a poor prognosis.[21] According to study of American society of clinical oncology done on 491 women, 79.6% tested negative for mutations in the BRCA 1 or BRCA 2 genes, 11.4% had a BRCA 1 mutation, 6.1% had a BRCA 2 mutation. Triple-negative breast cancer (negative estrogen receptor, progesterone receptor, and HER-2/neu status) was detected in 93 women. Of which 58.1% were BRCA negative, 34.4% were BRCA 1 positive, and 7.5% were BRCA 2 positive thus showing that BRCA1 carriers were more likely to be diagnosed with triple-negative breast cancer than noncarriers or BRCA 2 carriers (P<.001). When each receptor was examined alone, BRCA 1 associated cancers were more frequently ER and PR negative than were BRCA-negative (P< .001) but HER-2/neu expression did not differ significantly between mutation carriers and noncarriers (P=.06 and .23 respectively). It was also observed that BRCA 1 mutation carriers had higher nuclear grade tumors than did BRCA-negative women or BRCA 2 mutation carriers.[22] Emiliano Honrado et al in another study observed cancers associated with BRCA 1 are poorly differentiated infiltrating ductal carcinomas (IDCs) with higher mitotic counts and pleomorphism and less tubule formation than sporadic tumours as well as BRCA 1 tumours have been found to be more frequently estrogen receptor (ER) and progesterone receptor (PR) negative.[23]

Thus correlating ER, PR, Her-2/Neu and BRCA 1 will predict prognosis, diseae free survival, genetic inheritance and aid in treatment planning.

CONCLUSION

Carcinomas of breast should be subjected to immunohistochemistry to find out the status of hormone receptors for recommending required hormonal therapy. It is of utmost importance to correctly identify the subset of patients with positive cases so that they can avail benefit from the novel mode of therapy targeted therapy against the specific expression.

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