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Original Research Article

Study of GATA3 Expression in Breast Carcinomas

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Abstract:

Introduction: Among females, breast cancer is one of the most commonly diagnosed cancers and the leading cause of cancer death, followed by colorectal and lung cancer. Breast carcinoma is a very heterogeneous disease despite the common tissue of origin. GATA-binding protein 3 (GATA3) belongs to a family of 6 mammalian GATA dual zinc-finger transcription factors.

Methods: The study aims to evaluate the diagnostic value of GATA3 expression in breast carcinomas. 50 clinically and histologically proven cases of Invasive Breast cancers were taken into consideration and they were studied for GATA3 expression from 2017 to 2019 at MNJ Institute of Oncology, Hyderabad. The GATA3 expression was compared to estrogen receptor (ER), progesterone receptor (PR), and Her2 expression.

Results: Out of the total 50 selected cases, GATA3 was positive in 34 (n=34, 68%) of cases and negative in 16. GATA3 expression was seen in the majority (73.5%) of ER-positive cases (25) than in ER-negative cases (09) (p=0.0001). GATA3 expression was seen in 17 PR positive and 17 PR negative cases. GATA3 expression was more commonly seen in the Luminal A (44%) and B (06%) subtype, Her2 (06%) subtype and TNBC (12%). 100% of Grade 1 tumors showed GATA3 positivity, 75% of Grade 2 tumors and 59.3% Grade 3 tumors showed GATA3 positivity.

Conclusion: Like ER & PR, GATA3 is also commonly expressed in breast carcinomas and its expression has a favorable prognosis. GATA3 expression was commonly seen in Luminal A and B types of invasive breast cancers. GATA3 expression is seen in majority (73.5%) of only ER positive patients.

Keywords: Breast carcinoma, GATA3, IHC markers, Histopathology.

Introduction

Among females, breast cancer is the most commonly diagnosed cancer and the leading cause of cancer death, followed by colorectal and lung cancer. Breast carcinoma is a very heterogeneous disease despite the common tissue of origin [1].

A comprehensive molecular analysis of breast cancer revealed that TP53 (tumor proteinp53), PIK3CA (phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha), and GATA3 were the most frequently mutated genes, which significantly extends our knowledge of likely genomic drivers in breast cancer. [2]

GATA-binding protein 3 (GATA3) belongs to a family of 6 mammalian GATA dual zinc-finger transcription factors. In patients with breast cancer, the expression of GATA3 is closely related to estrogen receptor (ER) status and significantly associated with a favorable prognosis. GATA3 is the third most frequently mutated gene in breast cancer, with a mutation rate of approximately 10%. It is interesting to note that these mutations are observed for the most part in ER-positive tumors, suggesting the involvement of GATA3 mutations in the pathogenesis of luminal-like breast cancer.

Transcription factors or trans-acting factors are often organized in multigene families and play essential roles in activating target genes of specific cell fates by binding to their cognate DNA sequence to aid (and sometimes inhibit) RNA polymerase II (pol II) in locating the proper initiation site for transcription.

The GATA family of transcription factors, which is composed of six highly conserved transcription factors, binds a consensus DNA sequence (A/T) GATA (A/G) in the promoters of target genes via two zinc-finger domains with the consensus sequence CX2CX17CX2C to directly activate or repress target gene expression. [2,3]

GATA transcription factors play a wide role in the determination of cell differentiation and control of cell proliferation and movement. GATA1, GATA2, and GATA3 are expressed primarily in hematopoietic cells and are linked to their specification.

At the same time, GATA4, GATA5, and GATA6 play key roles in the specification of mesoderm and endoderm-derived tissues including the heart, intestines, and lungs.

In particular, GATA3 is also present in non-hematopoietic tissues including the kidneys, central nervous system, endothelial cells], and mammary gland, regulating their specification and differentiation.

During puberty, pregnancy, lactation, and involution in women, the mammary gland undergoes morphologic changes including cellular proliferation, differentiation, and apoptosis. GATA3 plays a vital role in orchestrating the lineage determination and maturation of these cells by directing mammogenesis toward a luminal cell fate. It also has prognostic value in breast carcinomas. [3,4]

Aim and Objectives

Aim: To study the diagnostic value of GATA3 expression in breast carcinomas.

Objectives:

1. To correlate GATA3 expression with histopathological grade.
2. To evaluate the significance of GATA3 expression in breast carcinomas

Materials and Methods

Study Design: Both prospective and retrospective study was done.

Period of Study: Total cases were amassed over two years, i.e. from June 2017 to June 2019.

Place of Study: MNJ Institute of Oncology and Regional Cancer Centre, Osmania Medical College, Hyderabad.

Sample Size: The total no. of cases studied was 50.

- Various Invasive breast malignancies were retrieved and were subjected to ER, PR, HER2 IHC and categorized into 4 subtypes (Luminal A, Luminal B, HER2 type, and TNBC) based on the steroid hormone receptor status.
- 50 cases were randomly selected from these 4 subtypes.
- Then GATA3 immunoexpression was studied amongst these 50 selected cases.

Inclusion Criteria: All clinically and histologically proven cases of Invasive Breast cancers

Exclusion Criteria:

- Benign lesions of the breast on histopathologic examination.
- Carcinoma In situ cases.

Method:

The specimens were fixed in 10% neutral buffered formalin. They were examined grossly according to the standard guidelines and sections were taken from representative sites.

These sections were then processed in an automated tissue processor and embedded in paraffin wax. 4-5-micron thickness sections were prepared from the corresponding paraffin blocks, one on albumin-coated slide for Haematoxylin and Eosin (H&E) staining and the others on poly-L-lysine coated slide for immunohistochemical staining. (ER, PR, HER2, GATA3).

Method of Immunohistochemical Staining: The kits for ER, PR, Her-2/neu & GATA3 immunohistochemical staining was obtained. The staining was done according to the manufacturer's protocol.

Reagents: The ER, PR, Her2, and GATA3 antibodies were ready to use vials. The following antibody clones were used:

- ER – obtained from BioGenex EP1 Rabbit monoclonal antibody in PBS with carrier protein and preservative.
- PR – obtained from BioGenex EP2 Rabbit monoclonal antibody in PBS with carrier protein and preservative.
- Her2 – obtained from BioGenex EP3 Rabbit monoclonal antibody in PBS carrier protein and preservative.
- GATA3 -obtained from Pathnsitu Mouse monoclonal antibody, L50-823 clone in PBS carrier protein and preservative.

IHC Results

- ER, PR, GATA3 are Nuclear stain while Her-2 neu is a Membranous stain. The slides were then examined under microscope to determine the reactivity pattern. Positive – tumor cells showing Brown stain in nucleus (ER, PR,) and complete membrane staining (Her-2 neu) is considered positive. The reactivity pattern was scored according to the guidelines of ASCO/CAP.
- Diagnosed cases of breast carcinoma are taken as control for GATA3.

This study is considered significant as P value is <0.001.

Results

The Institute received a total of 1580 invasive breast malignancy specimens over a period of 2yrs.Based on the ER PR & HER2 status these cases were categorized into 4 molecular Subtypes i.e. Luminal A, Luminal B, HER2 type and TNBC.50 cases were randomly selected from these 4 subtypes. GATA3 immunoexpression was correlated and studied in these total 50 selected cases. Out of the total 50 selected cases GATA3 was positive in 34 (n=34, 68%) of cases and negative in 16 (n=16,32%). The mean age among the GATA3 positive group was around 52 years, range being 27-72 years. The youngest patient was 27 years while the oldest was 72 years. The common age group range being 51-60years. Among the ER Positive and Negative cases, GATA3 expression was seen in majority (73.5%) of ER positive cases (25) than ER negative cases (09) (p=0.0001). GATA3 expression was seen in 17 PR positive and 17 PR negative cases.

Table 1:

GATA3	ER positive	ER negative	Total
GATA positive	25	09	34
GATA negative	02	14	16
Total	27	23	50

Table 2:

GATA3	PR positive	PR negative	Total
GATA positive	17	17	34
GATA negative	14	02	16
Total	31	19	50

Table showing GATA3 expression compared with Her2 expression

Table 3:

Her-2	GATA3 Positive	GATA3 Negative	Total
Negative	11	09	20
Score 2+	09	03	12
Score 3+	13	05	18
Total	33	17	50

The p value was statistically not significant.

Among the molecular subtypes, GATA3 expression was more commonly seen in Luminal A (44%) and B (06%) subtype, Her2 (06%) subtype and TNBC (12%). 17.6% of total GATA3 positive tumors were Grade1, 26.4% were Grade 2,55.8% were grade3.

100% of Grade 1 tumors showed GATA3 positivity,75% of Grade 2 tumors and 59.3% Grade 3 tumors showed GATA3 positivity

Discussion

Breast cancer (Breast CA) is the most frequently encountered cancer in females worldwide accounting for nearly a quarter (25%) of all cancers with an estimated 1.67 million new cases diagnosed in 2012. Women from less developed countries have a greater number of cases (883,000 cases) when compared to more developed (794,000) regions. [2]

ER-positive status is generally associated with a more favorable prognosis, but more importantly, it is a predictive marker of response to hormonal therapies such as tamoxifen and aromatase inhibitors. [3] However, ER-positive tumors represent a large and heterogeneous subgroup, and treatment decisions are most often based on clinicopathologic features such as tumor grade and lymph node status. Novel biomarkers can be used to further refine prognostic models, and some may be useful to predict response to adjuvant treatment. [4]

In the present study, out of the 50 selected Invasive Breast Carcinoma cases, GATA3 was positive in 68% of the cases and negative in 32% of the cases. Many studies have shown that like ER and PR, GATA3 is also quite commonly expressed in breast malignancies. Overall, In the present study, GATA3 immunoexpression was found in 68% of the cases. Similarly, in a study conducted by Ismail et al. 72% positive GATA3 expression cases were seen. [5]

In the present study, among the GATA3 positive cases, the age ranged from 27- 72 years. The mean age was around 52 years. The common age group range is 51-60 years. According to the present study it was found that GATA3 positivity was associated with a higher age group i.e., the majority of the cases were in the sixth decade of life. Ismail et al. found a mean age of 65 years in their study which was comparable to the present study. [5]

Ismail et al. found GATA-3 immunostaining positivity in 88% of cases of group 1, which were ER and PR positive. [5] The present study showed

73% ER-positive cases showing GATA3 positivity. Previous studies agreed that GATA-3 is among the best predictors of ER-positive status with a reported expression of 87.7% by Hoch et al. [6], 72% by Yang et al.[7], and 89% by Lehmann et al.[8] . However, they suggested that GATA-3 mRNA expression has a strong association with ER status. Regarding group 2, that is, ER and PR negative, they found that 56% of the cases showed positive GATA-3 expression. Reports of GATA-3 expression in ER-negative breast carcinomas varied between 16% in a study done by Hoch et al.[6]

According to Yoon et al, GATA3 as a continuous variable, they found that low protein expression was associated with high tumor grade, larger tumor size, negative estrogen receptor (ER) status, and negative progesterone receptor (PR) status. These associations were consistent when they repeated the analysis with GATA3 as a dichotomized variable. The only exception was that low GATA3 was no longer significantly associated with negative PR status. Because GATA3 expression was associated with tumor grade and hormone receptor status, they grouped patients by ER status or by tumor grade and examined GATA3 expression levels in these subpopulations. Notably, they found that lower levels of GATA3 were still predictive in a subset of individuals who had ER-positive tumors. [9]

Only a few studies have established a relationship between GATA3 expression and molecular subtypes of breast carcinoma. Jiang et al.[10] and Ismail et al.[5] Both show increased GATA3 expression in Luminal A, B cases followed by HER2 subtype and TNBC. The present study showed GATA3 expression at 44% in Luminal A, 6% in Luminal B, 6% in HER2, and 12% in the TNBC subtype.

The present study in concordance with Yoon et. al. [9] and Liu et al. [7] studies shows that the majority of the GATA3-expressing tumors were either of low or intermediate grade rather than high grade. Expression of GATA3 was 100% in Grade 1, 75% in Grade 2, and only 55.8% in Grade 3 in the present study.

Limitations

The following were the Limitations of the present study that could be worked upon in the future:

- The duration of the study and the number of cases could have been increased.
- The tumor size could be compared with the GATA3 positivity
- The nodal status and recurrences of the tumor at the same site or distant sites could be studied and compared
- Owing to the short time frame, the disease-free survival and overall survival could not be assessed.

Conclusion

Like ER & PR, GATA3 is also commonly expressed in breast carcinomas and has a favorable prognosis. GATA3 expression was commonly seen in Luminal A and B types of invasive breast cancers.

Furthermore, expression of GATA3 was also seen in a subset of HER2 type and Basal-like cancers which are considered to be hormone receptor-negative breast cancers. GATA3 expression is seen in the majority (73.5%) of only ER-positive patients. In patients who do not respond to Tamoxifen therapy despite ER positivity, GATA3 can help in determining the grade of tumor thus helping the clinician to change the therapy. To conclude GATA3 expression was significantly related to older age at diagnosis, well differentiated, less aggressive tumors with the majority showing Ductal morphology.

GATA3-positive tumors were associated with lower grades. This finding raises the possibility that targeting the GATA3 pathway may represent a novel therapeutic approach to the management of patients with GATA3-positive breast cancers particularly in TNBC, which has an otherwise inferior prognosis. The present study shows the benefit of adding GATA3 to the existing marker panel of breast cancers, to be able to predict response to therapy & open up new therapeutic options. High-grade tumors can be identified and treated appropriately, thus decreasing the mortality and morbidity

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