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Original Article

What GATA-3 told us in breast carcinoma? 2 Years of single tertiary center experience

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Abstract

Aim: Our study aims to find the relationship between the degree of GATA-3 expression in breast cancer and other prognostic factors such as ER, PR, HER-2, Ki67, and axillary metastasis.

Materials and Methods: The cases in which GATA-3 immunohistochemical staining was applied to breast cancer tissues between 2018 and 2020 were detected. Immunohistochemically stained preparations of ER, PRG, GATA-3, Ki-67, and HER-2 of these cases were obtained from the hospital archive and evaluated by two pathologists.

Results: As a result, GATA-3 was directly proportional to PR and ER and inversely proportional to Ki 67. GATA-3 expression was associated with a higher Ki-67 mitotic index compared to the percentage of ER and PR expression.

Conclusion: According to the results of our study, indicating GATA-3 positivity and negativity as well as the degree of expression in the pathology reports of breast tumors will help the clinician in terms of differentiation and prognosis of the tumor. Finally, breast tumors with high GATA-3 loss should be evaluated as more primitive tumors and the patients with these tumors should be followed up more closely.

Keywords: Breast carcinoma; GATA-3; prognostic factors

INTRODUCTION

GATA binding protein 3 is one of the six members of the GATA family of zinc-finger transcription factors that recognize a specific nucleotide sequence in the promoter region of target genes (1).

GATA-related genes are involved in the complex regulatory pathways and the development of mammary glands and thymocytes (2,3).

More specifically, GATA-3 plays an essential role in regulating mammary-gland morphogenesis and luminal cell differentiation and has been identified to play an important role in tumor initiation. GATA-3 is required for luminal cell differentiation of glands in breast tissue development. (3,4).

GATA-3 is used in daily pathology practice as a primary tumor marker for breast and urothelial carcinomas, especially in metastatic tumors, and for typing in kidney and salivary gland tumors. (5-8).

Despite its multi-specific nature, loss of function in the GATA-3 gene has recently been associated with the breast cell maturation loss and poor prognosis in breast cancers (3,9-10).

Our study aimed to present our 2-year single-center experience by correlating our GATA-3 immunohistochemical staining results in breast cancer patients with relation of the other prognostic parameters.

MATERIALS and METHODS

The cases in which GATA-3 immunohistochemical staining was applied to breast cancer tissues between 2018 and 2020 were detected. Immunohistochemically stained preparations of ER, PRG, GATA-3, Ki-67, and HER-2 of these cases were obtained from the hospital archive and evaluated by two pathologists.

The entire tissue was examined in the immunohistochemically stained preparations of ER, PR, Ki 67, and GATA-3; nuclear stained cells were accepted as positive and a 100-point scoring was made for each case. The lymph node metastasis status of the cases was obtained from the hospital information system.

Patients whose ER, PR, GATA 3, and 67 immunohistochemical stains were not in the archive were

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scored two by HER-2 immunohistochemical staining and whose metastasis status was unknown were not included in the study. Ki 67 was grouped as 1 between 0 and 15, 2 between 15 and 50 and 3 between 50 and 100. GATA-3 was classified into 4 groups as 1 between 0-25%, 2 between 25% and 50%, 3 between 50% and 90%, and 4 over 90%. ER and PR percentages were grouped as 0-1-2-3 as specified in the CAP protocol. If the score of HER-2 immunohistochemical stain was 3 positive (3+), HER-2 was considered positive, but if the score was 1 or 0 it was considered negative. The ones with the score of 2 positive (2+) were not included in the study. Biopsy or histopathological examination of the axillary dissection material was scored 1 if metastasis was present and scored 0 if metastasis was not present. Those with unknown metastasis status in the hospital system were not included in the study.

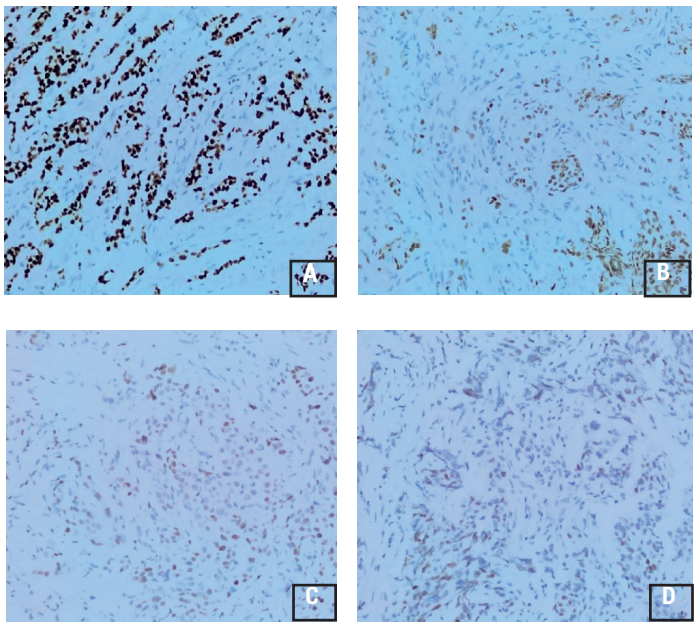

Figure 1. GATA 3 expression patterns in breast carcinoma; diffuse and dense expression (>%90 positive) (A), partial intensity loss (%50-90 positive) (B), partial intensity and prevalence loss (%25-50 positive) (C), prominent intensity and prevalence loss (%0-25 positive) (D)

Statistical Analysis

Mean and standard deviation were given as descriptive statistics for numerical variables, and frequency and percentage values were given for ordinal variables. Relationships between numerical variables were evaluated using Pearson's correlation coefficient. Relationships between ordinal variables were evaluated using the Goodman-Kruskal Gamma coefficient. Analyzes were performed using Jamovi 1.6.3 and R 4.0.3 programs. A value of p <0.05 was considered significant.

RESULTS

Sixty-four female patients between the ages of 27 and 74 were included in our study. The ER, PRG, HER-2, Ki-67, and GATA-3 values and histological subtypes of breast tumor tissues of the patients were summarized in Table 1. GATA-3 immunohistochemical staining patterns are shown in the Figure 1. According to our results, while the loss of GATA-3 expression increased there was a decrease in ER and PR expression and an increase in the Ki-67 index in the comparison of paired groups in the Pearson's correlation analysis (p <0.01) (Tables 2,3,4).

Table 1. Descriptive findings of ER, PR, HER-2-metastasis Ki 67, and metastasis statue of breast cancers

	N	%
ER		
+1	5	53
+2	5	8
+3	34	8
0	20	31
PR		
+1	2	3
+2	9	14
+3	29	45
0	24	37.5
HER-2		
Positive	26	40
Negative	38	60
Ki67		
0-15% (1)	11	17
15-50% (2)	42	66
50-100% (3)	11	17
Mean(%)	30.5±22	
GATA-3		
4+	34	53
3+	16	25
2+	9	14
1+	4	6
0	1	1.5
Metastasis statue		
Metastasis exist	51	
Metastasis absent	13	
Histological subtype		
Invasive breast carcinoma (NOS)	58	90
Mucinous	3	5
Lobular	1	1.5
Neuroendocrine	1	1.5
Encapsulated papillary	1	1.5

ER: The estrogen receptor, PR: Progesterone receptor, HER-2:Herceptin-2, NOS: Not other specified

Table 2. GATA-3 and ER compliance table

	ER			
GATA-3	**0**	**1**	**2**	**3**
0	1 (%5)	0	0	0
1	4 (%20)	0	0	0
2	6 (%30)	0	2 (%40)	1(%3)
3	6 (%30)	3(%60)	2 (%40)	5(%15)
4	3 (%15)	2(%40)	1(%20)	28(%82)

ER: Estrogen receptor, PR: Progesteron receptor

Table 3. GATA 3, ER, PR, Ki 67 values of the cases		
	Mean (%)	SD (±)
Gata-3	71.8	32.3
ER	55.5	44.3
PR	39.4	39.2
Ki 67	30.5	22.69
ER: Estrogen receptor, PR: Progesteron receptor		

Table 4. Pearson correlation values between the ER, PR, GATA-3, and Ki 67 parameters of the cases		
	Gata-3	Ki-67
ER	0.66*	0.4*
PR	0.66*	0.4*
Ki-67	-0.54*	
*p<0.001; ER: Estrogen receptor, PR: Progesteron receptor		

The number of metastatic patients was 51 and the number of non-metastatic patients was 13. While no GATA-3 loss was observed in 9 (69%) of 13 non-metastatic patients 26 metastatic patients had GATA-3 loss. According to our results, no relationship was found between GATA-3 and metastatic status (p >0.01).

Of the cases in our study, 26 were HER-2 positive and 38 were HER-2 negative. While 58% (15/26) of HER-2 positive cases had GATA-3 loss %40 (15/38) of HER-2 negative cases had GATA-3 loss. Although the rate of positive cases was higher than the rate of negative cases there was no statistically significant relationship between HER-2 positivity, which was a poor prognostic factor, and loss of GATA-3.

There was no relationship between age and GATA-3 status. Most of the cases were invasive breast carcinoma of the nonspecific type (90%) and the statistical analysis results could not be obtained as the other types were very few in our series.

DISCUSSION

Breast cancer is an increasingly common type of cancer in our country as well as in the developing countries (12). We know that good and severe prognostic parameters in breast cancer affect the treatment and follow-up modalities. According to the Breast Tumor's Volume in the publication of the WHO Classification of Tumors, ER and HER-2 are used as prognostic markers in breast cancers. In addition to these, many immunohistochemical markers that may be related to the prognosis of breast cancer have been studied in literature (13-19). As such, there has been keen interest in the potential role of GATA-3 dysregulation in the pathogenesis of breast cancer (20).

In our study, GATA-3 expression in breast cancers was important as it analyzed its relationship with the other prognostic parameters.

According to our findings, GATA-3 expression was directly related with the ER and PR expression, inversely related with Ki-67 index and associated with good prognosis.

In the studies in literature, a correlation was found between ER and GATA-3 expression (21).

In our results, the correlation coefficient of GATA-3 expression compared with Ki 67, which was higher than ER, suggests that GATA-3 is at least as important as ER in terms of prognosis.

The relationship between GATA 3 and metastasis and HER-2 positivity, which are poor prognostic parameters, was not significant. This may be due to the retrospective nature of our study. In addition, the majority of the patients were metastatic and therefore, our patient distribution was not homogeneous.

In conclusion, we defined GATA-3 expression in breast cancers concerning the other good prognostic parameters (ER, PR) in our two years of experience. GATA-3 loss was associated with the poor prognostic parameter, Ki-67. Most of the studies in literature support our results (18).

According to our results, the loss of staining in GATA-3 expression was converted to the other poor prognostic factors (Loss of ER and PR expression and high Ki-67 labeling index) that we studied in breast tumors.

LIMITATIONS

The limitations of our study are as follows: The number of cases was low; the sampling was not homogenous; and it did not include the data on the treatment response. Further studies investigating the relationship of GATA-3 with the response to the treatment in breast carcinomas are needed. Since the materials used were obtained from the needle biopsies the relationship between the tumor's histological grade and the other prognostic factors such as tumor diameter and GATA-3 could not be evaluated.

CONCLUSION

According to the results of our study, indicating GATA-3 positivity and negativity as well as the degree of expression in the pathology reports of breast tumors will help the clinician in terms of differentiation and prognosis of the tumor. Finally, breast tumors with high GATA-3 loss should be evaluated as more primitive tumors and the patients with these tumors should be followed up more closely.

Competing Interests: The authors declare that they have no competing interest.

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REFERENCES

1. Ko LJ, Engel JD. DNA-binding specificities of the GATA transcription factor family. Mol Cell Biol 1993;13:4011-22.

2. Pai SY, Truitt ML, Ting CN, et al. Critical roles for transcription factor GATA-3 in thymocyte development. Immunity 2003;19:863-75.
3. Asselin-Labat ML, Sutherland KD, Barker H, et al. Gata-3 is an essential regulator of mammary-gland morphogenesis and luminal-cell differentiation. Nat Cell Biol. 2007;9:201-9.
4. Asselin-Labat ML, Sutherland KD, Vaillant F, et al. Gata-3 negatively regulates the tumor-initiating capacity of mammary luminal progenitor cells and targets the putative tumor suppressor caspase-14. Mol Cell Biol 2011;31:4609-22.
5. Miettinen M, McCue PA, Sarlomo-Rikala M, et al. GATA3: a multispecific but potentially useful marker in surgical pathology: a systematic analysis of 2500 epithelial and nonepithelial tumors. Am J Surg Pathol 2014;38:13-22.
6. Brunelli M, Erdini F, Cima L, et al. Proximal CD13 Versus Distal GATA-3 Expression in Renal Neoplasia According to WHO 2016 Classification. Appl Immunohistochem Mol Morphol 2018;26:316-23.
7. Schwartz LE, Begum S, Westra WH, et al. GATA3 immunohistochemical expression in salivary gland neoplasms. Head Neck Pathol 2013;7:311-5.
8. Liu H, Shi J, Wilkerson ML, et al. Immunohistochemical evaluation of GATA3 expression in tumors and normal tissues: a useful immunomarker for breast and urothelial carcinomas. Am J Clin Pathol 2012;138:57-64.
9. Mehra R, Varambally S, Ding L, et al. Identification of GATA3 as a breast cancer prognostic marker by global gene expression meta-analysis. Cancer Res 2005;65:11259-64.
10. Yoon NK, Maresh EL, Shen D, et al. Higher levels of GATA3 predict better survival in women with breast cancer. Hum Pathol 2010;41:1794-801.
11. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394-424.
12. Auvinen P, Tammi R, Kosma VM, et al. Increased hyaluronan content and stromal cell CD44 associate with HER2 positivity and poor prognosis in human breast cancer. Int J Cancer 2013;132:531-9.
13. Furuya M, Horiguchi J, Nakajima H, et al. Correlation of L-type amino acid transporter 1 and CD98 expression with triple negative breast cancer prognosis. Cancer Sci 2012;103:382-9.
14. Witkiewicz AK, Dasgupta A, Sammons S, et al. Loss of stromal caveolin-1 expression predicts poor clinical outcome in triple negative and basal-like breast cancers. Cancer Biol Ther 2010;10:135-43.
15. He J, Peng R, Yuan Z, et al. Prognostic value of androgen receptor expression in operable triple-negative breast cancer: a retrospective analysis based on a tissue microarray. Med Oncol 2012;29:406-10.
16. Liu CG, Lu Y, Wang BB, et al. Clinical implications of stem cell gene Oct-4 expression in breast cancer. Ann Surg 2011;253:1165-71.
17. Nagai MA, Gerhard R, Fregnani JH, et al. Prognostic value of NDRG1 and SPARC protein expression in breast cancer patients. Breast Cancer Res Treat 2011;126:1-14.
18. de Kruijf EM, Sajet A, van Nes JG, et al. HLA-E and HLA-G expression in classical HLA class I-negative tumors is of prognostic value for clinical outcome of early breast cancer patients. J Immunol 2010;185:7452-9.
19. Baptista MZ, Sarian LO, Derchain SF, et al. Prognostic significance of PD-L1 and PD-L2 in breast cancer. Hum Pathol 2016;47:78-84.
20. Tan PH, Ellis I, Allison K, et al. WHO Classification of Tumours Editorial Board. The 2019 World Health Organization classification of tumours of the breast. Histopathology 2020;77:181-5.
21. Shaoxian T, Baohua Y, Xiaoli X, et al. Characterisation of GATA3 expression in invasive breast cancer: differences in histological subtypes and immunohistochemically defined molecular subtypes. J Clin Pathol 2017;70:926-34.