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Can GATA3 Immunocytochemistry be Utilized as a Reliable Diagnostic Marker for Metastatic Breast Carcinoma in Cytological Materials?

A Comparative Study with Mammaglobin and GCDFP-15 Expression

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ABSTRACT

Objective: Cytomorphologic differentiation of metastatic breast carcinoma from non breast metastases in cytological materials can be difficult. Current breast immunocytochemical markers have low sensitivities. Transcription factor GATA3 is a promising marker for detecting breast differentiation in cytological materials. The aim of the study was to assess the diagnostic value of GATA3 as a breast differentiation marker in metastatic cytological materials and to compare it with expression of mammaglobin and gross cystic disease fluid protein-15 (GCDFP-15).

Material and Method: We retrospectively retrieved 133 cases of metastatic breast carcinoma from the archive the of Cytology Unit between December 2013 and June 2015. They included 77 fine needle aspiration and 56 serous effusion samples. Forty-five cytological materials from non mammary metastatic tumors were used as a control. Immunostaining was performed on cell blocks for the presence of GATA3, mammaglobin and GCDFP-15.

Results: GATA3 nuclear staining was detected in 82.7% of metastatic breast carcinomas, and 11.1% of metastatic non mammary adenocarcinomas ($p < 0.001$). GATA3 sensitivity, specificity, positive predictive value, negative predictive value and accuracy were 82.7%, 88.9%, 95.7%, 63.5% and 84.3%, respectively. Mammaglobin and GCDFP-15 staining of metastatic breast carcinoma cases was positive in 70.7% and 47.1%, respectively. GATA3 staining was significantly higher compared with mammaglobin and GCDFP-15 ($p< 0.001$).

Conclusion: GATA3 is more sensitive marker than mammaglobin and GCDFP-15 for diagnosing metastatic breast carcinoma in cytological cell block materials. Adding mammaglobin to GATA3 resulted in improvement in its sensitivity. GATA3 was occasionally positive in some metastatic non mammary carcinoma that may cause misdiagnosis.

Key Words: GATA3, Immunostaining, Metastatic breast carcinoma, Cytology

INTRODUCTION

About one third of patients with breast carcinoma have evidence of metastatic spread during the course of disease. Although the exact incidence of metastatic breast carcinoma has not been estimated, it has been reported that 162 thousand females in the United States lived with metastatic disease in 2013. This was assessed by oncologists who encountered cases of metastatic tumor in patients with breast cancer (1). In the majority of metastatic cases, a history of primary tumor is well known. However, some cases initially present with metastases of unknown primary. It is very important to identify the primary site of origin to apply the optimal therapy (2). As breast cancer is one of the commonest malignancies affecting females worldwide, primary breast carcinoma usually enter the differential diagnosis of metastatic carcinoma in females, even in the absence of breast complaints (3). Differentiation between metastatic breast and non breast carcinomas in Papanicolaou-stained cytological slides can be a challenging mission due to lack of histological architecture and low cellularity. Immunocytochemical (ICC) markers can more accurately confirm breast differentiation. Currently used markers, mammaglobin and gross cystic disease fluid protein-15 (GCDFP-15) are specific but have variable sensitivity results (4). GATA3 is one of six zinc-finger transcription factors. It is vital for proliferation and differentiation of several tissues and is expressed in many tumors (5). Recently, GATA3 was reported to be a very sensitive marker for breast carcinomas (6). Decreased GATA3 level has been associated with a worse outcome (7).

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To our knowledge, the number of studies that evaluate the diagnostic utility of GATA3 staining in cytological materials of primary or metastatic breast carcinoma is limited.

The aim of the study was to assess the diagnostic utility of GATA3 immunocytochemistry in detecting the breast origin of metastatic sites in cytological materials and to compare GATA3 expression with those of conventional and commonly used breast markers; mammaglobin and GCDFP-15.

MATERIALS and METHODS

Cytopathology reports from the Cytology archives of the National Cancer Institute in Cairo, Egypt, during the period between December 2013 and June 2015 were searched retrospectively for the keywords "metastatic breast carcinoma". One hundred and thirty three cases were recognized. They included seventy seven fine needle aspiration cytology (FNAC) materials and fifty six exfoliated serous effusion samples. Inclusion criteria included: a) cases which had cytological reports of metastatic carcinoma, b) cases which had previous documented histories of primary breast carcinoma that were confirmed either by prior histopathological diagnosis of excised breast lump or prior cytopathological diagnosis of aspirated primary breast mass and c) absence of any other detectable primary tumors on routine metastatic follow up, d) availability of adequate formalin-fixed, paraffin-embedded cell block materials for ICC study. As a control group, 45 cytological materials from well recognized non mammary metastatic tumors were also analyzed for GATA3 staining. A minimum of four Papanicolaou stained slides and a cell block section were prepared for each case. All included archival slides were reviewed to confirm the diagnosis and to assess adequacy of cell blocks in order to use ICC. The presence of at least 5 groups with at least 5 metastatic tumor cells within each group was considered to be adequate cell block materials and was included in the current study (4).

Immunocytochemical Staining and Assessment

A 4-µm section was cut from each paraffin-embedded cell block and mounted onto positively charged slides. The slides were subjected to the ICC technique using a streptavidin-biotin-peroxidase according to the manufacturer's protocol. The immunostaining was accomplished with BenchMark XT automated slide stainer (a product of Ventana Medical Systems). Sections were deparaffinized, rehydrated and treated with 0.3% H2O2 for 5 min to block endogenous peroxidase activity. They were then exposed to heat-induced antigen retrieval. Antibody against GATA3 (mouse monoclonal antibody, clone (L50-823), CELL MARQUE, Ventana Medical System was used. Diaminobenzidine was used as a chromogen and Mayers hematoxylin as a counterstain. Materials of metastatic breast carcinoma were also assessed for mammaglobin staining using rabbit monoclonal antibody, clone (31A5) as well as GCDFP-15 using rabbit monoclonal antibody, clone EP1582Y; CELL MARQUE, Ventana Medical System. Appropriate positive and negative control slides were prepared. Negative control for all immunostaining was prepared by substituting the primary antibodies with Phosphate Buffered Saline (PBS). Positive staining control for GATA3 included sections of urothelial carcinoma. Positive staining controls for mammoglobin and GCDFP-15 included sections of breast carcinoma known to be positive to these markers. Only nuclear staining for GATA3 was scored, while cytoplasmic staining for mammaglobin and GCDFP-15 was reported. For GATA3, mammaglobin and GCDFP-15, staining intensity and percentage of stained cells were reported. Staining intensity was scored as 0 (no staining), 1+ (weak), 2+ (moderate), or 3+ (strong). Immunostained slides were also assessed with respect to the percentage of stained cells (0, no stained cells; 1+, 1%-10% of cells were stained; 2+, 11%-50% of cells were stained; 3+, >50% of cells were stained). The final score was calculated by adding the percentage of positive cells to intensity; a total score more than 2 was considered as a positive staining result, and a combined immunoreactivity score less than or equal to 2 was considered a negative result (8).

Statistical Analysis

Data was analyzed using GraphPad Prism version 7.00 for Windows (GraphPad Software, La Jolla, CA, USA: www.Graphpad.com). Statistical significance was determined by Fisher's exact and Chi-square analysis for categorical variables and ANOVA for numerical variables. The level of significance was set at 0.05 or less. In addition, the sensitivity, specificity, Positive predictive value (PPV), Negative predictive value (NPV) and accuracy of the marker were calculated.

RESULTS

Clinicopathologic Characteristics of the Cases

One hundred and thirty three cytological materials of metastatic breast carcinoma were assessed for positivity of GATA3 immunostaining in cell block materials. All the studied cases were female. The mean age was 44±10.3 with range from 35 to 81 years; the median age was 55 years. They included seventy-seven FNAC materials and fifty-six exfoliated serous effusion samples. FNAC were aspirated from the following anatomical metastatic sites: 42 from lymph nodes (23 axillary, 16 cervical and 3 mediastinal), 18

from subcutaneous lump, 10 from lung lesions and 7 from liver mass. Serous effusion materials included 40 pleural and 16 ascitic effusions. Of 133 cases, 98 cases (73.7%) had previous surgical resection of primary breast carcinomas and documented histopathological reports. Histopathological subtypes were ductal carcinoma (n=73), lobular carcinoma (n=18), papillary carcinoma (n=3), mucinous carcinoma (n=3) and metaplastic carcinoma (n=1). The remaining 35/133 cases had previous final cytopathological reports of mammary carcinoma aspirated from primary breast lumps; 30 were ductal carcinoma, 4 lobular and one was papillary carcinoma. As a control group, cytologic materials from 45 metastatic tumors from other non mammary defined sites were also analyzed for GATA3 staining. These materials included 11 metastatic carcinomas from the female genital tract, 10 from the thyroid gland, 9 of lung origin, 7 from the gastrointestinal tract, 7 from the pancreas and one from the urinary bladder.

GATA3 Immunocytochemical Staining on Metastatic Cytological Materials

Positive GATA3 nuclear staining was detected in 82.7% of metastatic breast carcinomas (110 of 133 cases). The majority of stained cases, 85 cases (77.3%), had a score of 6 or 5 (Figure 1-3). Twelve cases had a score of 4 while thirteen cases had a score of 3 (Figure 4) (Table I).

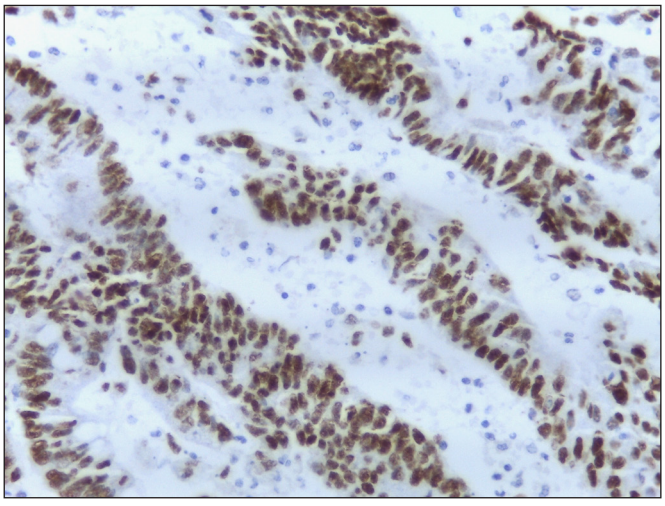

Figure 1: GATA3 immunocytochemical staining in cytological cell block from metastatic papillary breast carcinomas in axillary lymph nodes, score 6 (IHC; x200).

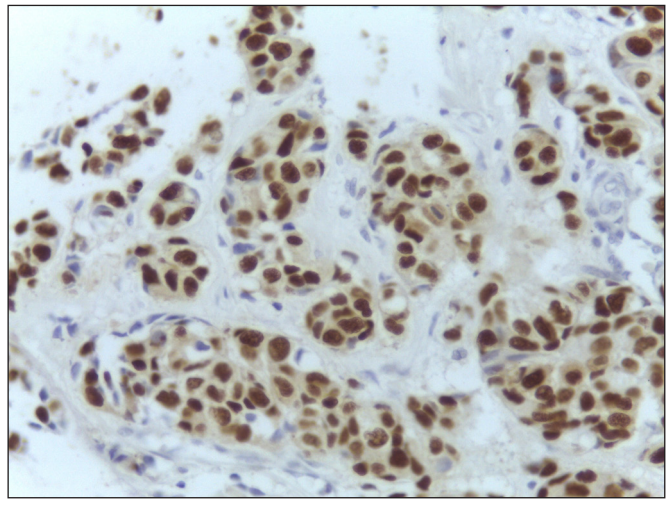

Figure 2: GATA3 immunocytochemical staining in cytological cell block from metastatic ductal breast carcinomas in pleural fluid, score 6 (IHC; x400).

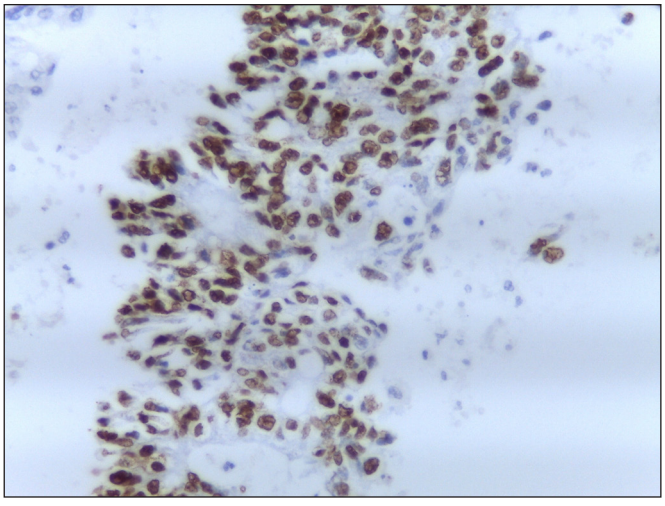

Figure 3: GATA3 immunocytochemical staining in cytological cell block from metastatic lobular breast carcinomas in cervical lymph node, score 6 (IHC; x400).

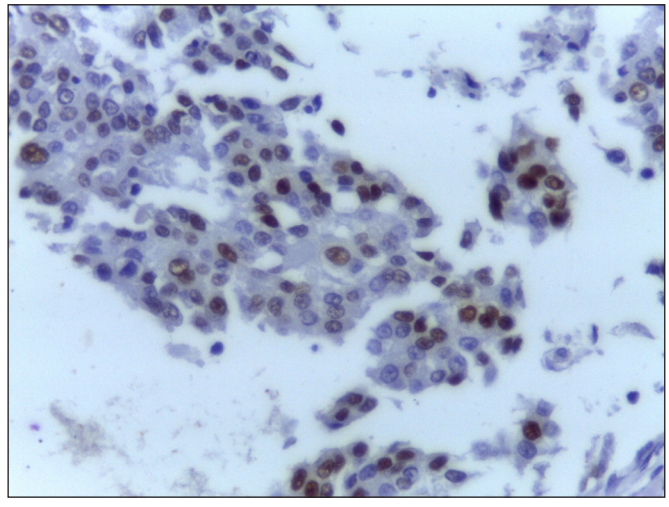

Figure 4: GATA3 immunocytochemical staining in cytological cell block from metastatic ductal breast carcinomas in supraclavicular lymph node, score 3 (IHC; x400).

Five out of 45 (11.1%) non mammary metastatic adenocarcinomas were positive for GATA3; two positive cases were metastatic carcinoma from lung to cervical lymph nodes while two cases were metastatic uterine and ovarian carcinoma in ascitic fluid and supraclavicular lymph nodes, respectively. The remaining case was metastatic urothelial carcinoma to subcutaneous tissue. They had scores of 3 and 5 (Table I). GATA3 was not detectable in any metastases from thyroid carcinoma as well as gastrointestinal tract and pancreatic adenocarcinoma.

Sensitivity of GATA3 for identifying breast primary origin in metastatic tumors was 82.7% (95% confidence interval [CI]: 75.3% to 88.3%) while the specificity for absence of breast differentiation in metastatic tumors was 88.9% (95% CI: 76.1% to 95.65). Positive predictive value (PPV) was 95.7% (95% CI: 90% to 98.4%). Negative predictive value (NPV) was 63.5% (95% CI: 51.1% to 74.3%). The overall accuracy was 84.3% (95% CI: 78.2% to 88.9%) (Table II). A statistical significant difference was demonstrated between GATA3 staining in metastatic breast and non breast carcinomas cases ($p < 0.001$). No GATA3 staining was detected in benign cells set in the background (inflammatory cells, mesothelial cells or stromal cells). No significant background staining was reported. GATA3 staining results among different breast carcinoma histological subtypes were reported in Table III. No statistical difference was detected between GATA3 staining and different main breast histological subtypes ($p > 0.05$).

GATA3 Immunocytochemical Staining Compared to Mammaglobin and GCDFP-15 Expressions

Assessment of other conventional breast markers, mammaglobin and GCDFP-15, were carried out on metastatic breast carcinoma cell blocks to compare their results with that of GATA3. Mammaglobin staining was positive in 94 out of 133 cases (70.7%). GATA3 staining for metastatic breast carcinoma was significantly higher compared with mammaglobin staining ($p = 0.03$). Mammaglobin staining tended to be less diffuse and less intense than GATA3; forty-six out of 94 mammaglobin positive metastatic breast carcinomas (48.9%) demonstrated scores of 6 and 5 (Figure 5) (Table IV). The difference was significant ($p < 0.001$). GATA3 and mammaglobin values were concordant in 93 of 133 cases (69.9%); 82 cases were GATA3 positive / mammaglobin positive and 11 cases were GATA3 negative / mammaglobin negative.

Table I: GATA3 immunostaining scores among positive metastatic cases sorted by primary sites

Primary sites of metastasis	Total	GATA3 positive cases	Immunostaining scores			
			3	4	5	6
Breast	133	110	13	12	30	55
Female genital tract	11	2	2	0	0	0
Lung	9	2	1	0	1	0
Urinary bladder	1	1	0	0	1	0

Table II: Relation between GATA3 staining results and primary sites of metastases

Primary site of metastasis	GATA3		Total
	positive	negative	
Mammary primary site	110	23	133
Extra-mammary primary sites	5	40	45

Table III: GATA3 staining results among different breast carcinoma subtypes

Histological / cytological breast carcinoma subtypes	Total no.	GATA3 positivity
Ductal carcinoma	103	85 (82.5%)
Lobular carcinoma	22	20 (90.9%)
Papillary carcinoma	4	2 (50%)
Mucinous carcinoma	3	3 (100%)
Metaplastic carcinoma	1	0 (0%)
Total	133	110

Table IV: Distribution of immunocytochemical scores of GATA3, mammaglobin and GCDFP-15 among positive metastatic breast cases

Score	GATA3 positivity No.	Mammaglobin positivity No.	GCDFP-15 positivity No.
3	13	15	9
4	12	33	7
5	30	20	5
6	55	26	3
Total	110/133	94/133	24/51

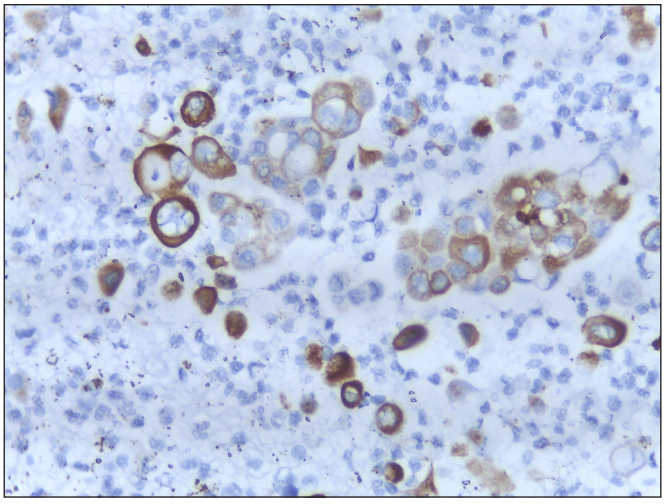

Figure 5: Mammaglobin immunocytochemical staining of metastatic breast carcinoma cell block in subcutaneous nodule, score 5 (IHC; x400).

Discordant results were found in 40 of 133 cases (30.1%). Of these, GATA3 was positive and mammaglobin was negative in 28 cases. GATA3 was negative and mammaglobin was positive in 12 cases. Adding mammaglobin to GATA3 resulted in improvement in GATA3 sensitivity to reach 91.7% for identifying the breast primary.

After staining of GATA3 and mammaglobin, 51 of 133 metastatic breast carcinoma cell blocks had sufficient material for further evaluation of GCDFP-15. Among these 51 cases, GATA3 expression was detected in 40 (78.3%). On the other hand, 24 cases (47.1%) were positive for GCDFP-15 with background staining in 9 cases. All GCDFP-15 positive cases were positive for GATA3. Sixteen cases were GATA3 positive but GCDFP-15 negative. The remaining 11 cases were negative for both markers. GATA3 staining for metastatic breast carcinoma was significantly higher compared with GCDFP-15 staining ($p < 0.001$). Diffuse and intense staining was detected in only 8 cases (33.3%) of GCDFP-15 positive metastatic breast carcinomas (Table IV). Adding GCDFP-15 to GATA3 resulted in no improvement in GATA3 sensitivity.

DISCUSSION

Although a metastatic tumor is an advanced stage cancer and considered fatal, proper treatment can relieve tumor-related symptoms, delay cancer progression, prolong life and improve the quality of life (9). It makes a big therapeutic and outcome difference when the primary organ of metastasis is well known (10). Identification of breast differentiation in metastatic sites, based on morphology, is a diagnostic challenge. The most commonly used markers, mammaglobin and GCDFP-15, tend to be specific but have low sensitivity and can be difficult to interpret in small samples (4). GATA3 is a promising marker for breast differentiation. Although GATA3 expression has been well studied in histological specimens, the use of GATA3 in cytological materials is understudied (11). The main focus of the current study was to evaluate GATA3 as a diagnostic marker for metastatic breast carcinoma in cytological materials.

In the current work, positive GATA3 nuclear staining was detected in 82.7% of metastatic breast carcinomas (110/133). In the literature, the GATA3 positivity rate has been reported to range from 75 to 100% (12- 14). The reasons of this wide range might be related to the number of studied cases or sample preparation (cell block or direct smear). Leng et al., in their 2017 work reported GATA3 positivity in 71% of cell block sections and 89% of smear samples (13). They reported that cell block materials are more reliable as optimal samples for immunostaining in cytological materials because fixation and staining procedures are similar to that used for histologic samples. The differences in GATA3 expression rates between the published studies might have also resulted from using different antibody clones or scoring systems (15). Different sensitivities of using different clones on breast resection specimens were reported in previous reports (16, 17). Other contributing factors for expression variation could also be related to tumor characteristics (grade and molecular subtypes) or technical causes (antigen retrieval methods, dilutions or incubation times) (8). Furthermore, in the

present study, GATA3 expression demonstrated a diffuse and intense staining pattern (score 6 and 5) in 77.3% of positive cases, suggesting that GATA3 expression was evenly distributed with minimal staining variation within the tumor. Therefore GATA3 can reliably highlight tumor cells in samples with dispersed cells among a normal or reactive background. Our result was in accordance with previous reports (4,8).

On the other hand, GATA3 staining demonstrated relatively high specificity (88.9%) in the present work. Five out of 45 (11.1%) non mammary metastatic carcinomas were positive for GATA3. A statistically significant difference was demonstrated between GATA3 staining in metastatic breast and non breast carcinoma cases ($p < 0.001$). These findings agreed with others who reported that a small but significant percentage of metastatic non mammary, non urothelial carcinoma can express GATA3 (8,13). Thus they recommended using the GATA3 marker as a part of panels to exclude or confirm other non breast origin. Others reported that all the studied non breast, non urothelial metastatic carcinomas were negative (9,15). In our study, 2/9 (22.2%) of metastatic carcinoma from the lung and 2/11 (18.2%) of metastatic female genital tract carcinoma were GATA3 positive. These percentages were higher than that reported in the literature on surgical specimens (18). This might be due to small numbers of cases in the current work and difference in materials used. Because metastatic adenocarcinomas from the lung and female genital tract have cytomorphological overlapping features with metastatic breast carcinoma, cytopathologists should be aware of GATA3 staining in such tumors to avoid misinterpretation.

In the present study, no statistical difference was detected between GATA3 staining and various main breast histological subtypes ($p > 0.05$). This result was in keeping with that reported by others (12,15). In the present work, no GATA3 expression was detected in the benign cells set in the background. Some authors observed weak positivity in a minority of benign lymphoid cells in some cases (4,9). In surgical specimens, positivity in a considerable percentage of reactive and malignant mesothelial cells was observed (18). In other studies, no GATA3 expression was detected in such cells (9,13).

Another aim of the current work was to compare the positivity of GATA3 with that of mammaglobin and GCDFP-15. In our study, GATA3 staining revealed superior sensitivity compared to the sensitivities of mammaglobin and GCDFP-15, the difference was statistically significant ($p = 0.03$ and $p < 0.001$, respectively). These results were in accordance with previously published studies (4,8,15). If the three markers were used in a panel, adding mammaglobin to GATA3 markers resulted in improvement of GATA3 sensitivity (91.7%) as it could identify 12 additional cases that were GATA3 negative. Adding GCDFP-15 to GATA3 showed no sensitivity improvement. Therefore, GATA3 could be used as a panel with the mammaglobin marker for breast differentiation. Others have agreed with these results (9,19). Based on experience with cytological materials, markers with nuclear staining (such as GATA3) are superior to those with cytoplasmic staining such as mammaglobin and GCDFP-15 (1,13). Less background staining of GATA3 adds new advantages over the other two markers (15).

In conclusion, GATA3 is a sensitive marker for diagnosing metastatic breast carcinoma in cytological cell block materials. GATA3 is more sensitive than mammaglobin and GCDFP-15 with more diffuse and stronger expression. Adding mammaglobin to GATA3 resulted in improvement of the sensitivity. GATA3 was occasionally positive in some metastatic non mammary carcinomas that might be included in breast differential diagnosis; sole GATA3 staining should therefore be interpreted in conjunction with morphological, clinical, radiological findings to avoid a misdiagnosis when working with a tumor of unknown origin or used as part of an immunostaining panel. However, it is recommended to use GATA3 in a large number of non mammary metastatic tumors on cytological materials to detect its exact incidence in these tumors.

CONFLICT of INTEREST

The authors declare no conflict of interest.

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