2015 Cancer Cytopathology Young Investigator Challenge Nominee

Original Article

Young Investigator Challenge: The Utility of GATA3 Immunohistochemistry in the Evaluation of Metastatic Breast Carcinomas in Malignant Effusions

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BACKGROUND: It is not uncommon to encounter challenges in the immunohistochemical confirmation of metastatic breast cancer given the limited sensitivities of mammaglobin and gross cystic disease fluid protein 15 (GCDFP-15/BRST-2) and the significant proportion of triple-negative breast carcinomas (ie, tumors that are negative for estrogen receptor [ER], and progesterone receptor [PgR], and human epidermal growth factor 2 [HER2]). GATA binding protein 3 (GATA3) has emerged as a potentially useful immunohistochemical adjunct during the evaluation of metastatic breast carcinomas in cytology specimens. The objective of the current study was to examine GATA3 expression in the context of malignant effusions secondary to both mammary and extramammary malignancies. **METHODS:** In total, 306 malignant effusions (from 62 metastatic breast carcinomas and 244 extramammary malignancies) were examined using GATA3 immunohistochemistry. Effusions with metastatic breast carcinoma were also examined using immunohistochemistry for additional breast markers (ER, PgR, HER2, mammaglobin, and GCDFP-15/BRST-2). **RESULTS:** GATA3 immunohistochemistry highlighted the tumor cells in 58 of the 62 samples (93.5%) from patients with metastatic breast carcinoma, which was higher than the observed sensitivity of immunohistochemistry for ER (63.8%), PgR (41.4%), HER2 (15.5%), mammaglobin (22.4%), and GCDFP-15/BRST-2 (5.2%). GATA3 expression also was observed in a subset of malignant effusions secondary to extramammary primaries, specifically, in 28 of 244 specimens (11.5%). **CONCLUSIONS:** GATA3 is a highly sensitive marker for the detection of metastatic breast carcinomas in effusion specimens. However, this marker is not entirely specific for malignancies of breast origin. Thus, GATA3 should be used in conjunction with additional immunohistochemical markers during the cytologic evaluation of malignant effusions. ***Cancer (Cancer Cytopathol)* 2015;123:576-81**. © *2015 American Cancer Society.*

KEY WORDS: breast; cancer; carcinoma; cytology; GATA3; immunohistochemistry; malignant effusion.

INTRODUCTION

GATA binding protein 3 (GATA3) is a member of the zinc finger transcription factor family that recognizes (A/T)GATA(A/G) nucleotide sequences in target gene promoters to regulate gene transcription. GATA3 is involved in the normal development of breast epithelium, urothelium, and a subset of lymphocytes. GATA3 has recently been reported as a sensitive marker for breast malignancies on surgical resection specimens.[1–3] GATA3 and estrogen receptor (ER) are involved in a cross-regulatory loop and are frequently coexpressed in breast carcinomas; however, several studies have demonstrated that subsets of "triple-negative" breast carcinomas (ie, negative for ER, and progesterone receptor [PgR], and human epidermal growth factor 2 [HER2]) also stain positively for GATA3.[2–4] This has important implications for confirming metastatic breast carcinoma in patients who have primary and/or metastatic tumors that are negative for ER, PgR, and HER2. Furthermore,

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given the limited sensitivities of gross cystic disease fluid protein 15 (GCDFP-15/BRST-2) and mammaglobin immunohistochemistry for detecting breast carcinomas,[5] additional immunohistochemical markers for detecting metastatic breast carcinoma warrant investigation.

Studies examining the utility of GATA3 immunohistochemistry in cytologic specimens are limited in their number and scope, and such evaluations have primarily focused on comparing the effectiveness of GATA3 immunohistochemistry to other breast immunomarkers. The utility of GATA3 immunohistochemistry has been highlighted particularly in pleural effusions, as breast carcinoma is a common source of metastasis to the pleural fluid. In pleural effusion specimens, GATA3 is reportedly more sensitive than both GCDFP-15/BRST-2 and mammaglobin as a marker for metastatic breast cancer.[5,6] GATA3 is also well recognized as a sensitive marker for urothelial carcinoma, which is helpful in patients with metastatic carcinoma for whom differential diagnostic considerations include metastatic urothelial carcinoma, prostatic adenocarcinoma, and pelvic squamous cell carcinoma.[7] More recent studies in surgical resection specimens reported GATA3 positivity in other malignancies, including mesotheliomas, pancreatic adenocarcinomas, and pulmonary adenocarcinomas.[8,9]

In light of the above-mentioned contributions to the literature, we sought to expand the scope of GATA3 immunohistochemical evaluation to a large series of malignant effusions. Specifically, we examined the sensitivity of GATA3 as a marker for detecting metastatic breast carcinomas in effusion specimens, including triple-negative breast carcinomas. Furthermore, we examined a variety of metastatic carcinomas of extramammary origin to better understand the specificity of GATA3 immunohistochemistry.

MATERIALS AND METHODS

This study was approved by the Institutional Review Board at University of Michigan. The electronic pathology database was searched to identify consecutive patients who had metastatic carcinoma diagnosed in pleural, pericardial, and peritoneal effusion specimens at the University of Michigan between January 1, 2008 and December 31, 2012. Electronic medical records also were examined to assist in determining the primary etiology of malignant cells for each case evaluated in this study. The cytology slides were retrieved from the archive, and the hematoxylin and eosin-stained cell block sections were reviewed to evaluate cellularity. Immunohistochemistry for GATA3 was performed on cell block material for all malignant cases that had adequate tumor cellularity (>20 tumor cells).

GATA3 immunohistochemistry was performed on all specimens using formalin-fixed, paraffin-embedded cell blocks sectioned at 5-micron thickness using the Dako Autostainer (Dako, Carpinteria, Calif). Heat-induced epitope retrieval was performed using the Dako FLEX Target Retrieval Solution high-pH antigen-retrieval buffer, pH 9.01, for 20 minutes. After quenching of endogenous peroxidases, the anti-GATA3 mouse monoclonal antibody (clone L50-823; 1:100 dilution; Cell Marque, Rocklin, Calif) was applied at room temperature for 30 minutes. The FLEX horseradish peroxidase EnVision System was used for detection. Then, 3,3′-diaminobenzidine (DAB) chromogen was applied for 10 minutes. Slides were counterstained with Harris hematoxylin for 5 seconds, dehydrated, and coverslipped.

Samples of metastatic breast carcinoma were also evaluated by immunohistochemistry for ER, PgR, HER2, GCDFP-15/BRST-2, and mammaglobin. The details are summarized in Table 1. Anti-ER rabbit monoclonal antibody (clone SP1; 1:50 dilution; Cell Marque) was applied at room temperature for 20 minutes, rabbit monoclonal anti-PgR antibody (clone Y85; 1:40 dilution; Cell Marque) was applied at room temperature for 20 minutes, and anti-HER2 rabbit monoclonal antibody (clone SP3; 1:150 dilution; Cell Marque) was applied at room temperature for 20 minutes. Mouse monoclonal antibodies against GCDFP-15/BRST-2 (clone D6; Signet; Dedham, Mass) and mammaglobin (clone 304-1A5; Dako) were applied at a dilution of 1:1000 each on separate sections. The FLEX + rabbit or mouse EnVision System was used for detection, and the DAB chromogen was applied for 10 minutes. Slides were counterstained with Harris hematoxylin for 5 seconds and were subsequently dehydrated and coverslipped.

Immunostained slides were scored with respect to the intensity (0, no staining; 1+, weak staining; 2+, moderate staining; 3+, strong staining) and extent (0, no cells stained; 1+, 1%-10% of cells stained; 2+, 11%-50% of cells stained; 3+, >50% of cells stained) of tumor cell staining. The sum of the 2 scores represented the combined immunoreactivity score; a total score >2 was

TABLE 1. Summary of Antibodies Used in this Study

Antibody	Clone (Host)	Dilution	Epitope Retrieval	Detection
GATA3	L50-823 (mouse)	1:100	FLEX TRS[a]	EnVision[a]
ER	SP1 (rabbit)	1:50	FLEX TRS	EnVision
PgR	Y85 (rabbit)	1:40	FLEX TRS	EnVision
HER2	SP3 (rabbit)	1:150	FLEX TRS	EnVision
Mammaglobin	304-1A5 (mouse)	1:1000	FLEX TRS	EnVision
GCDFP-15/ BRST-2	D6 (mouse)	1:1000	None	EnVision

Abbreviations: ER, estrogen receptor; GATA3, GATA binding protein 3; GCDFP-15/BRST-2, gross cystic disease fluid protein 15; HER2, human epidermal growth factor receptor; PgR, progesterone receptor; TRS, target-retrieval solution.
[a] The EnVision System and FLEX TRS are both from Dako (Carpinteria, Calif).

considered a positive staining result, and a combined immunoreactivity score ≤ 2 was considered a negative result.

RESULTS

In total, 355 specimens of malignant pleural, peritoneal, and pericardial effusions with adequate tumor cellularity in the cell block preparations were identified. Of these, 49 represented duplicate samples from patients, leaving a total of 306 patient specimens for analysis in this study. Cell block sections derived from all 306 of these specimens were first assessed by GATA3 immunohistochemistry, including 62 specimens from breast primaries and 244 from extramammary primaries. The subtypes of the primary breast cancers were known in 60 of the 62 patients with metastatic breast carcinoma (47 ductal, 10 lobular, and 3 mucinous carcinomas). Our observations with regard to GATA3 expression in all of the examined cases are summarized in Table 2.

Eighty-six of 306 specimens (28.1%) scored positive for GATA3 expression in tumor cells, and the positive specimens were not restricted to metastatic breast cancers (Table 2). Fifty-eight of the 86 GATA3-positive malignant effusions were derived from breast primaries; thus, the sensitivity of GATA3 immunohistochemistry for detecting metastatic breast carcinoma was 58 of 62 specimens (93.5%). The remaining 28 GATA3-positive malignant effusions were observed in metastases secondary to extramammary primaries, including Mullerian, lung, pancreatobiliary, urothelial, gastric, esophageal, thyroid, and germ cell primaries (Table 2). All 3 effusions involved by urothelial cell carcinoma were positive for GATA3.

TABLE 2. GATA Binding Protein 3 Immunohistochemical Analysis for 306 Malignant Effusions Sorted by Primary Site

Primary Site	Total No. of Cases	No. of GATA3-Positive Cases (%)
Breast	62	58 (93.5)
Ductal	47	43 (91.5)
Lobular	10	10 (100)
Mucinous	3	3 (100)
Unknown	2	2 (100)
Mullerian	109	8 (7.3)
Serous adenocarcinoma	83	7 (8.4)
Clear cell adenocarcinoma	6	0 (0)
Endometrioid adenocarcinoma	2	0 (0)
Mucinous adenocarcinoma	1	0 (0)
Mixed epithelial adenocarcinoma	3	0 (0)
Undifferentiated carcinoma	3	0 (0)
Carcinosarcoma	4	0 (0)
Endocervical adenocarcinoma	1	0 (0)
Not otherwise specified[a]	6	1 (16.7)
Lung	44	6 (13.6)
Adenocarcinoma	38	5 (13.2)
Squamous cell carcinoma	2	1 (50)
Small cell carcinoma	4	0 (0)
Upper gastrointestinal tract	24	3 (12.5)
Esophageal adenocarcinoma	12	1 (8.3)
Gastric adenocarcinoma	12	2 (16.7)
Pancreatobiliary tract	26	3 (11.5)
Pancreatic adenocarcinoma	18	2 (11.1)
Cholangiocarcinoma	8	1 (12.5)
Colorectal adenocarcinoma	14	0 (0)
Unknown primary	13	2 (15.4)
Renal cell carcinoma	5	0 (0)
Urothelial carcinoma	3	3 (100)
Testicular germ cell tumor	2	2 (100)
Thyroid	2	1 (50)
Papillary thyroid carcinoma	1	0 (0)
Anaplastic carcinoma	1	1 (100)
Hepatocellular carcinoma	1	0 (0)
Penile squamous cell carcinoma	1	0 (0)

Abbreviation: GATA3, GATA binding protein 3.
[a] In these specimens, tumor subtyping was precluded by either the lack of subsequent resection specimens (n = 4), lack of residual carcinoma for evaluation on resection specimen (n = 1), or lack of pathology report in a patient who had a remote history of Mullerian adenocarcinoma (n = 1).

There were 2 malignant effusions secondary to testicular primaries—a yolk sac tumor and a choriocarcinoma—each of which was positive for GATA3. Other primaries, such as tumors of primary lung, Mullerian, or pancreatobiliary origin, had a lower proportion of specimens that were positive for GATA3 (Table 2). Two of the 28 GATA3-positive malignant effusions were derived from carcinomas of unknown primaries in patients who had no documented history of breast cancer. As GATA3 immunohistochemistry was negative in 216 of 244 malignant effusions secondary to extramammary primaries, the specificity of GATA3 immunohistochemistry was 88.5%.

The distribution of composite GATA3 scores, which we determined by evaluating the extent and intensity of

TABLE 3. Immunohistochemical Scoring Distribution of GATA Binding Protein 3-Positive Cases

Primary Site	Total No. of Positive Cases	Combined Immunoreactivity Score: No. of Positive Cases (%)			
		6	5	4	3
Breast	58	53 (91.4)	1 (1.7)	3 (5.2)	1 (1.7)
Lung	6	3 (50)	1 (16.7)	1 (16.7)	1 (16.7)
Mullerian	8	2 (25)	3 (37.5)	3 (37.5)	—
Urothelial	3	3 (100)	—	—	—
Pancreatobiliary	3	2 (66.7)	—	1 (33.3)	—
Gastric	2	—	—	1 (50)	1 (50)
Unknown	2	—	—	2 (100)	—
Esophageal	1	—	1 (100)	—	—
Thyroid	1	—	—	1 (100)	—
Germ cell	2	1 (50)	—	1 (50)	—

GATA3 expression, according to primary site is displayed in Table 3. Diffuse and strong GATA3 staining (composite score = 6) was observed in the majority of GATA3-positive malignant effusions secondary to breast primaries (53 of 58 effusions; 91.4%) and in all urothelial primaries (3 of 3 effusions; 100%) (Fig. 1). However, diffuse and strong GATA3 immunoreactivity also was observed in occasional effusions from metastatic carcinomas of extramammary origin (Fig. 1). Other GATA3-positive specimens in effusions from extramammary malignancies, such as gastric, esophageal, and thyroid carcinomas, demonstrated lower intensity and/or extent of staining for GATA3.

After analysis by GATA3 immunohistochemistry, 58 of 62 effusion specimens from metastatic breast carcinomas had sufficient remaining tumor cell material in the cell block for further evaluation of additional breast cancer-relevant immunohistochemical markers (ER, PgR, HER2, GCDFP-15/BRST-2, and mammaglobin). Of the 4 effusion specimens that had insufficient cellularity for further immunohistochemical analysis, 2 were negative for GATA3 expression, 1 had a composite GATA3 score of 4, and the remaining specimen had a composite GATA3 score of 6. Of the 58 effusion specimens from metastatic breast carcinomas that had sufficient cellularity, 56 were positive for GATA3 (96.6%), 37 were positive for ER (63.8%), 24 were positive for PgR (41.4%), 9 were positive for HER2 (15.5%), 13 were positive for mammaglobin (22.4%), and 3 were positive for GCDFP-15/BRST-2 (5.2%) (Table 4). Of note, in 11 of the 58 effusions from metastatic breast carcinomas (19%), GATA3 was the only positive marker. In the 2 GATA3-negative effusions from metastatic breast cancer, all of the other breast markers were also negative in the tumor cells.

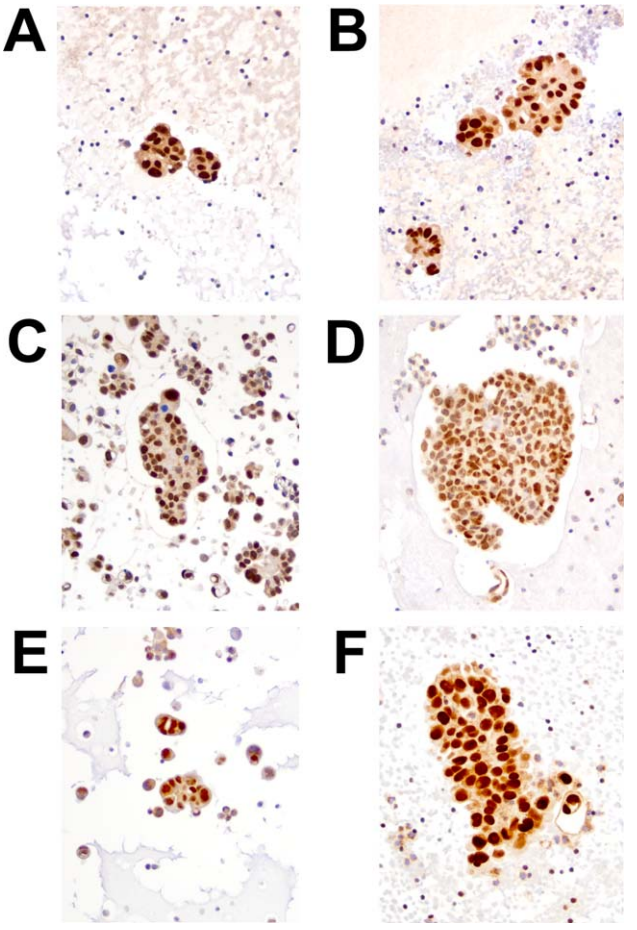

Figure 1. Representative photomicrographs illustrate GATA binding protein 3 (GATA3) expression on immunohistochemistry in effusion specimens from metastatic carcinomas of breast and extramammary origin. Nuclear GATA3 expression is observed in (A,B) 2 metastatic breast carcinomas, (C) a lung carcinoma, (D) a Mullerian carcinoma, (E) a pancreatic carcinoma, and (F) and a urothelial cell carcinoma (original magnification × 200 in A-F). Note that the nuclei of lymphocytes in the background can also demonstrate nuclear GATA3 expression, and this can serve as an internal positive control.

TABLE 4. Breast Cancer Immunohistochemical Marker Analysis of 58 Malignant Effusions Secondary to Breast Primaries

Marker	No. of Positive Cases (%)	Combined Immunoreactivity Score: No. of Positive Cases			
		6	5	4	3
GATA3	56 (96.6)	51	2	2	1
ER	37 (63.8)	29	7	1	—
PgR	24 (41.4)	7	4	8	5
HER2	9 (15.5)	5	4	—	—
Mammaglobin	13 (22.4)	2	3	2	6
GCDFP-15/ BRST-2	3 (5.2)	—	—	2	1

Abbreviations: ER, estrogen receptor; GATA3, GATA binding protein 3; GCDFP-15/BRST-2, gross cystic disease fluid protein 15; HER2, human epidermal growth factor receptor; PgR, progesterone receptor.

TABLE 5. Breast Cancer Immunohistochemical Marker Analysis Categorized by Receptor Profile of Breast Primaries

Breast Primary Receptor Profile	Immunohistochemical Marker: No. of Positive Cases (%)		
	GATA3	Mammaglobin	GCDFP-15/ BRST-2
ER+/PgR+/ HER2+, n = 3	3 (100)	0 (0)	0 (0)
ER+/PgR+/ HER2−, n = 29	29 (100)	6 (20.7)	3 (10.3)
ER+/PgR−/ HER2+, n = 6	6 (100)	1 (16.7)	0 (0)
ER+/PgR−/ HER2−, n = 6	6 (100)	2 (33.3)	0 (0)
ER−/PgR−/ HER2+, n = 1	1 (100)	0 (0)	0 (0)
ER−/PgR−/ HER2−, n = 13	11 (84.6)	4 (30.8)	1 (7.7)

Abbreviations: −, negative; +, positive; ER, estrogen receptor; GATA3, GATA binding protein 3; GCDFP-15/BRST-2, gross cystic disease fluid protein 15; HER2, human epidermal growth factor receptor; PgR, progesterone receptor.

A summary of GATA3, mammaglobin, and GCDFP-15/BRST-2 expression in our cohort of 58 metastatic breast carcinomas categorized by the receptor profile of the patients' breast primaries is provided in Table 5. Note that 11 of 13 triple-negative breast primaries were positive for GATA3 (84.6%), most of which had a composite immunoreactivity score of 6 (90.9%).

DISCUSSION

GATA3 has previously been cited as a useful marker for identifying malignancies of breast and urothelial origin. In a study by Braxton et al,[10] 86% of breast carcinomas were positive for GATA3 in fine-needle aspiration and serous effusion specimens, whereas mammaglobin and GCDFP-15 had lower sensitivities (26% and 14%, respectively). Their study corroborates our findings, as 93.5% of our effusions from metastatic breast carcinoma were positive for GATA3.

It is noteworthy that previous reports of GATA3 positivity were low in cytologic specimens from patients with triple-negative breast cancers (ie, tumors negative for ER, and PgR, and HER2). Braxton et al reported that all ER-positive cytology specimens with breast cancer were positive for GATA3, but all specimens from triple-negative breast cancers were negative for GATA3 expression.[10] However, in our current study, 11 of 13 malignant effusions (85%) involved by triple-negative breast primaries were positive for GATA3. These findings agree with more recent studies on GATA3 expression in triple-negative breast resection specimens published by Krings et al, who reported GATA3 expression in 44% to 66% of primary triple-negative breast carcinomas, depending on the subtype of GATA3 antibody used.[11]

Furthermore, most of the GATA3-positive, triple-negative metastatic breast carcinoma specimens in our study demonstrated a diffuse and intense staining pattern for GATA3; specifically, 15 of 18 GATA3-positive, triple-negative specimens (83%) demonstrated a composite immunoreactivity score of 6. This supports the notion that GATA3 is a particularly useful marker for helping to confirm a diagnosis of metastatic breast carcinoma, including triple-negative cancers, in effusion specimens given the lower overall sensitivities for mammaglobin and GCDFP-15/BRST-2. It is worth noting that a review of the composite immunoreactivity scores of the other breast immunomarkers in our study revealed that the majority of composite scores for GCDFP-15/BRST-2 and mammaglobin were ≤ 4 (Table 4). It may be helpful to keep this in mind, particularly for cell block preparations that have limited tumor cellularity. In such specimens, the patchy distribution of staining for mammaglobin and GCDFP-15/BRST-2 could further contribute to the limited sensitivity and utility of these markers in confirming the involvement of a malignant effusion by a breast primary.

However, caution must be exercised in patients who have malignant effusions from unknown primaries or in

those who have a clinical suspicion of a second, distinct primary. Although GATA3 positivity may be supportive of the involvement of an effusion by a breast primary, the findings in our study also demonstrate that a small but significant proportion of other common etiologies of malignant effusions also exhibit a range of GATA3 positivity, including Mullerian, pancreatobiliary, lung, and upper gastrointestinal tract primaries. Therefore, we acknowledge that it is prudent to use immunohistochemistry for GATA3 as part of a panel that includes other immunohistochemical markers to help rule in or rule out these other primary sites. For instance, immunohistochemistry for thyroid transcription factor-1 and Napsin-A can be helpful in identifying metastatic lung adenocarcinoma in effusions.[12–14] Furthermore, paired box 8 (PAX8) can be used to identify metastatic carcinomas of renal, thyroid, and Mullerian origin.[14–16] In this study, it is noteworthy that there was 1 case each of a malignant effusion involved by a testicular choriocarcinoma and yolk sac tumor, both of which were positive for GATA3, with GATA3 composite scores of 6 and 4, respectively. These tumors are less common and are rarely encountered in the setting of malignant effusions. Nonetheless, these instances further highlight the limitation of the utility of GATA3 in isolation.

In summary, the high sensitivity of GATA3 immunohistochemistry renders this marker a useful adjunct in the diagnosis of malignant effusions secondary to metastatic breast carcinoma. Nonetheless, this marker should not be used in isolation; careful evaluation of the cytomorphology, clinical history, and radiologic findings, as well as the use of a panel of markers are important for the accurate characterization and diagnosis of malignant effusions.

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The authors made no disclosures.

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