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ORIGINAL ARTICLE

Utility of GATA3, mammaglobin, GCDFP-15, and ER in the detection of intrathoracic metastatic breast carcinoma

Kathryn S. Dyhdalo, MD[a], Christine N. Booth, MD[a], Jennifer A. Brainard, MD[a], Maureen C. Croyle, CT(ASCP)[a], Ashley M. Kolosiwsky, BS[a], Abha Goyal, MD[a], Thomas R. Gildea, MD, MS[b], Francisco A. Almeida, MD, MS[b], Aziza Nassar, MD[c], Jordan P. Reynolds, MD[a,*]

[a] *Pathology and Laboratory Medicine Institute, Cleveland Clinic, 9500 Euclid Avenue Cleveland, Ohio*
[b] *Department of Pulmonary Medicine, Respiratory Institute, Cleveland Clinic, Cleveland, Ohio*
[c] *Department of Pathology and Laboratory Medicine, Mayo Clinic, Jacksonville, Florida*

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Introduction Breast carcinoma (BC) metastatic to the intrathoracic cavity is difficult to diagnose due to low sensitivity of current immunohistochemical (IHC) stains. Mammaglobin, gross cystic disease fluid protein-15 (GCDFP-15), and estrogen receptor (ER) immunomarkers show variable results. GATA3 is a recently described marker for detecting urothelial and breast cancers. Our goal is to test the utility of GATA3 in cell blocks from thoracic cytology specimens.

Materials and methods We retrieved cases of BC that metastasized to the thoracic cavity from January 1, 2005 to September 30, 2013. IHC was performed on the cell blocks for the presence of GATA3, ER, GCDFP-15, and mammaglobin. Stains were scored quantitatively and qualitatively.

Results Fifty cases of metastatic BC found in pleural effusions and endobronchial ultrasound-guided fine-needle aspirates were identified in 48 patients. Thirty-four cases had sufficient material for IHC (19 pleural effusions, 15 endobronchial ultrasound-guided fine-needle aspirates). GATA3 showed strong nuclear positivity in 31 of 34 cases (91.2%). ER (25 of 34, 73.5%), mammaglobin (23 of 34, 67.6%) and GCDFP-15 (11 of 34, 32.6%) were positive in fewer cases. GATA3 and ER were concordant in 26 of 34 cases (76.5%) (24 ER/GATA3–positive, 2 ER/GATA3–negative). Discordant results were found in 8 of 34 cases (23.5%). Of these, GATA3 was positive and ER was negative in 7 cases. GATA3 was negative and ER was positive in 1 case.

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*Corresponding author: Jordan P. Reynolds, MD; Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195. Tel.: +1-216-444-4833; Fax: +1-216-445-3707.

E-mail addresses: Reynolj4@ccf.org, jpreyno@gmail.com (J.P. Reynolds).

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Conclusions GATA3 is more sensitive than ER, mammaglobin, or GCDFP-15 in detecting metastatic BC in cytologic specimens. GATA3 may be positive when ER is negative. In cytologic specimens with limited diagnostic material, GATA3 may be used as a first-line marker in a limited IHC panel to support metastatic BC.

Introduction

Breast cancer is the most common cause of cancer in women, with 235,050 expected new cases in 2014 in the United States. Lung cancer is the second most common cancer in women, with 224,210 new cases expected in 2014.[1] Whether a tumor is the result of metastasis or is a new primary tumor has important prognostic and treatment implications. Breast and lung adenocarcinomas can have similar morphologies, and the cytologic diagnosis of these 2 diseases poses the added challenge of limited tissue for further testing. Confirmation of metastatic breast carcinoma (BC) to the thoracic cavity from pleural effusion (PE) or endobronchial ultrasound-guided transbronchial fine-needle aspirates (EBUS-TBNA) is difficult to achieve due to the low sensitivity of currently available immunohistochemical (IHC) stains. Mammaglobin and gross cystic disease fluid protein-15 (GCDFP-15) show variable results.[2] GATA3 is a recently described marker that can be used to detect urothelial cancer and BC.[3-7] Our goal is to test its utility in cell blocks (CB) of PE or EBUS-TBNA specimens and compare its performance against classically and commonly used IHC stains.

Materials and methods

After obtaining Institutional Review Board approval, a search of the Anatomic Pathology CoPath Plus (Cerner Corporation, Kansas City, Mo) database from the Cleveland Clinic was conducted for PE and bronchoscopy cytology cases with a diagnosis of metastatic BC from January 1, 2005 to September 30, 2013. Cases with nonbreast carcinomas and atypical diagnoses were excluded.

CB were prepared using the thrombin-clot technique.[8] All specimens were fixed in formalin for $\geq$6 hours. IHC was performed on the paraffin-embedded CB for GATA3 (1:100 dilution; Biocare Medical, LLC, Concord, Calif), estrogen receptor ([ER] prediluted; Ventana Medical Systems, Inc, Tucson, Ariz), GCDFP-15 (1:3 dilution, Covance, Princeton, NJ), and mammaglobin (1:40 dilution; Cell Marque, Rockland, Calif).

Staining patterns were scored both quantitatively and qualitatively. Tumor cells were evaluated based on the number of nuclei (GATA3, ER) or cell cytoplasm (mammaglobin, GCDFP-15) stained as follows: 0, no staining; 1, <5% of tumor cells staining; 2, 5% to 25% staining; 3, 26% to 50% staining; and 4, >50% of tumor cells staining. Slides were also evaluated for intensity of IHC staining as follows: 0, no staining; 1, weak staining; 2, moderate staining; and 3, strong staining. Cases were considered positive if they showed any staining intensity (1 or higher) in any tumor cells (1 or higher). Staining patterns were correlated with tumor morphology on CB slides. Fisher exact testing was performed using JMP Pro 10 statistical software (SAS Institute Inc, Cary, NC).

Results

Fifty cases of BC in PE and EBUS-TBNA cases were identified in 48 patients (all female, ages 30-90 years, mean: 60 years). Thirty-nine cases had sufficient material present on the CB to perform IHC (23 PE, 16 EBUS-TBNA specimens) for ER, GATA3, mammaglobin, and GCDFP-15 staining. In some cases, a partial IHC panel was previously completed as part of the initial diagnostic workup (e.g., ER and mammaglobin may already have been present). After staining, 34 cases had sufficient tumor material remaining on each stained slide for evaluation (19 fluids, 15 bronchoscopic). The CB were recut and IHC stains were performed to complete the panel for the purpose of this study. All cases had surgical resections confirming their primary BC. Of these, 28 were infiltrating ductal carcinoma, 4 were infiltrating lobular carcinoma (1 pleomorphic lobular carcinoma), and 2 were infiltrating mammary carcinoma with mixed ductal and lobular features.

GATA3 stained the majority of metastatic BC (31 of 34 cases, 91.2%), which was significantly higher than the staining seen with either mammaglobin (23 of 34, 67.6%, $P = 0.0001$) or GCDFP-15 (11 of 34, 32.6%, $P = 0.0001$) (Table 1, Fig. 1). Table 2 shows the breakdown of tumor cell staining percentages and staining intensities. GATA3 staining showed intense, nuclear staining in a diffuse pattern. When positive, strong nuclear staining (2+ or more) was present in 30 of 31 cases (96.8%). ER often stained >50% of tumor cells (18 of 34, 53%), with even distribution between weak, moderate, and strong staining intensities. Mammaglobin, when positive, stained a focal area and was less intense than GATA3 staining. Of the 23 positive mammaglobin cases, 2 had weak staining, and in 6 cases, <5% of tumor cells were stained. Of the 11 positive GCDFP-15 cases, 2 had staining in <5% of tumor cells. Positive staining cases for GCDFP-15 showed an intensity of at least 2. GATA3 and ER were concordant in 26 of 34 cases (76.5%) (24 ER/GATA3−positive, 2 ER/GATA3−negative). Discordant results were found in 8 of 34 cases (23.5%). Of these, GATA3 was positive, while ER was negative in 7 cases (20%), and GATA3 was negative with a positive ER in 1 case (case 32). Three of 34 (8.8%) were triple negative breast cancers (ER, progesterone receptor,