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Original contribution

A combination of GATA3 and SOX10 is useful for the diagnosis of metastatic triple-negative breast cancer☆

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Summary In metastatic breast cancer (MBC), it can be difficult to establish the origin if the primary tumor is triple negative or if there is a loss of biomarker expression. SOX10 expression has been reported in primary triple-negative breast cancer but is poorly studied in metastatic lesions. In this study, the diagnostic utility of a panel of SOX10, GATA3, and androgen receptor (AR) in MBC negative for estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 was evaluated and compared with the expression of these markers in the matched primary breast cancer. In a series of 57 triple-negative MBCs, 82% were positive for GATA3, 58% for SOX10, and 25% for AR. Nearly all MBCs (95%) were positive for either GATA3 or SOX10, with 46% dual positive and 5% of cases negative for both markers. Most GATA3-negative MBC cases were SOX10 positive (70%). AR expression was only seen in GATA3-positive MBC (25%) and was significantly more frequent in SOX10-negative MBC (48%) versus SOX10-positive MBC (9%; $P = .001$). Concordance for GATA3, SOX10, and AR between the primary and metastasis was 89%, 88%, and 80%, respectively. Although GATA3 is a more sensitive lineage marker than SOX10 in MBC, SOX10 is a useful adjunct because it is positive in most GATA3-negative breast metastases. Using both GATA3 and SOX10 is recommended for confirming breast as the site of origin in metastases that lack estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 expression, whereas the addition of AR is not helpful.

1. Introduction

Breast cancer metastases are commonly encountered in clinical practice owing to the high prevalence of this disease and the high frequency that these lesions are surgically biopsied. Breast cancer is one of the most common cancers in the United States. Based on National Cancer Institute/Surveillance, Epidemiology, and End Results reporting, in 2016 new breast cancer diagnoses exceeded 266 000, with more than 40 000 breast cancer deaths reported [1]. The most significant cause of breast cancer mortality is due to metastatic progression. Risks for the development of metastases are related to several factors including primary tumor size, histologic grade, lymph node involvement, and tumor biology/biomarker status [2,3]. Breast cancer patients have a high

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likelihood of developing metastases, especially if diagnosed at an early age [4]. Accurate diagnosis of breast cancer metastases is critically important to facilitate clinical therapeutic decision making. Per current guidelines, those patients with clinically suspected breast cancer metastases who are surgically appropriate and have accessible lesions should be offered biopsy for confirmation of disease process, and for the reassessment of breast biomarkers estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) [5]. The diagnostic distinction of a suspected metastatic breast cancer (MBC) from a nonbreast malignancy is a very relevant clinical consideration. Published studies indicate that women who are diagnosed as having a primary breast cancer (PBC) have a relatively higher risk of developing a second nonbreast malignancy compared with women from the general population. This risk is highest within the first 10 years after the PBC diagnosis and in younger premenopausal patients [6].

The confirmation of a breast primary site of origin of a metastatic lesion is generally straightforward if (1) the patient has an established history of breast cancer, (2) histologic slides from the prior PBC are available to re-review for morphologic comparison to metastasis, (3) the metastasis shows stable expression of both breast lineage markers and biomarkers (ER/PR/HER2). However, in clinical practice, these favorable diagnostic conditions may not be present. It can be difficult to establish the origin of a putative breast metastasis if the primary tumor is either triple negative for breast biomarkers (ER/PR/HER2) or if there is a loss of biomarker expression in the metastasis. Likewise, the histologic slides from the prior PBC may not be practically available for re-review. In addition, a metastasis may represent the initial clinical presentation from an occult PBC.

It is important to note that the sensitivity of standard breast lineage markers is dependent on tumor subtype, with the lowest sensitivity observed in grade 3, ER-negative, and metaplastic breast cancers [7]. High-grade and triple-negative breast cancer (TNBC) can pose a diagnostic challenge because they may display both nonspecific histomorphologic features and immunophenotypic staining profiles. TNBC and basal-like breast cancers often do not show positivity for established standard breast lineage markers such as mammaglobin (17%-24%) and GCDFP-15 (0-5%) [8]. The reduced sensitivity of most breast lineage markers including GATA3 in TNBC can complicate the diagnosis of MBC [9]. In addition, the potential for loss of biomarker expression in MBC imposes a further diagnostic challenge, as ER/PR/HER2 status is not infrequently discordant between the primary and metastatic lesion [10].

The availability of more sensitive breast lineage markers that can reliably identify metastatic breast carcinoma that is triple negative for ER, PR, and HER2 would be of high clinical utility. Labeling of TNBC by SOX10 and androgen receptor (AR) has been recently described in primary TNBC. However, there are few publications that have examined their performance in MBC. Furthermore, no studies have directly compared the sensitivity of SOX10 with the standard breast lineage marker GATA3, specifically in the most clinically challenging context of working up metastatic TNBC. An assessment of the stability and concordance of these lineage markers between the primary and matched metastatic lesion is also lacking.

In this investigation, we evaluated the diagnostic utility of a panel of SOX10, GATA3, and AR in MBC that is negative for ER, PR, and HER2 and compared the expression of these markers with matched PBC.

2. Materials and methods

2.1. Case selection

After institutional review board approval, we conducted a retrospective search of the pathology database at our institution to identify MBC diagnosed from 2013 to 2017, which lacked expression of ER, PR, and HER2, and for which we had an available in-house PBC specimen. Outside consult cases were excluded. Clinicopathological data from the electronic medical record and pathology reports were collected. For PBC, this included specimen type (core needle biopsy and/or excision specimen), patient age at the time of PBC, histologic type, grade (1, 2, or 3), tumor size (cm), lymph node stage, ER (SP1; Spring, Pleasanton, CA) and PR (636; Dako, Santa Clara, CA) status (positive or negative, percent staining), HER2 immunohistochemistry (IHC; scores 0, 1+, 2+, and 3+), and fluorescence in situ hybridization results (positive, negative, equivocal, indeterminate, HER2/centromere enumeration probe for chromosome 17 [CEP17] ratio, HER2/cell, and CEP17/cell). For MBC, this included site of metastases; patient age at the time of metastatic biopsy; ER, PR, and HER2 results; and any other immunohistochemical results.

2.2. Immunohistochemistry

IHC was performed at The Ohio State University Wexner Medical Center. In our institution, all MBC specimens are tested for ER, PR, and HER2. Those cases that are HER2 equivocal by IHC are reflexed to HER2 fluorescence in situ hybridization (PathVysion; Abbot, Irving, TX) in accordance with the 2013 American Society of Clinical Oncology/College of American Pathologists HER2 guideline recommendations [11]. The frequency of IHC expression of SOX10 (Biocare, Pacheco, CA; clone BC34, dilution 1:200, antibody incubation 15 minutes, retrieval high pH for 20 minutes), GATA3 (Biocare; clone L50-823, dilution 0.319333, antibody incubation 15 minutes, retrieval high pH for 20 minutes), and AR (Dako, Santa Clara, CA; clone AR441, dilution 1:200, antibody incubation 15 minutes, retrieval high pH for 30 minutes) was assessed in both MBC and PBC specimens. Staining was performed on whole-slide sections from core needle biopsy and/or resection specimens. All 3 antibodies were stained using the Leica Bond III system, and deparaffinization and

epitope retrieval were performed using the Leica Dewax and ER2 solution (high pH), respectively. All 3 antibodies used the Leica Bond polymer refine detection kit. Slides were counterstained with hematoxylin and dehydrated before coverslipped. Any degree of nuclear labeling was scored and recorded as a percentage (0-100%). Nuclear staining was scored for all 3 markers; ≥1% nuclear positivity was considered a positive result. In those specimens in which GATA3, SOX10, or AR was performed at the time of clinical review, the original IHC stains were re-reviewed and scored. In specimens in which IHC stains GATA3, SOX10, or AR were not performed at the time of clinical review, additional IHC stains were performed on archived material where available.

2.3. Statistical analysis

Correlation between marker expressions was determined by Fisher exact probability and agreement between PBC and MBC by κ coefficient.

3. Results

A total of 898 in-house MBC specimens were identified in our database during the search period. Cases in which no prior in-house PBC cases were reviewed in our institution were excluded (n = 635). Of 263 MBC cases with matched in-house PBC specimens, 72 (27%) of the MBC cases were triple negative for ER, PR, and HER2. Of the 72 triple-negative MBC cases, 57 had adequate/available MBC tissue available and were included in the series. Of these 57 cases, 44 had adequate/available PBC tissue for analysis. Because several of the markers were not originally performed at the time of clinical review on all cases, additional IHC staining was required on archived material including GATA3 (39 PBC and 4 MBC), SOX10 (41 PBC and 32 MBC), and AR (41 PBC and 6 MBC). In total, GATA3 IHC results were available for 44 PBC cases and 57 MBC cases, SOX10 IHC results were available for 43 PBC cases and 57 MBC cases, and AR results available for 42 PBC cases and 56 MBC cases. Most cases included in this study were core needle biopsy specimens for both PBC (26/44) and MBC (40/57) specimens, the remainder consisted of resection specimens.

In our retrospective review, we identified a total of 57 cases of MBC diagnosed from 2013 to 2017 that lacked expression of ER, PR, and HER2. Metastatic sites include the bone (15), brain (14), lung (8), nonregional lymph node (6), liver (5), skin (4), and other (5). In all cases, the diagnosis of PBC preceded the diagnosis of metastatic progression. The mean interval between PBC and MBC was 3.1 years (range, 0-16 years). The mean age of patients at the time of MBC was 54 years (range, 26-81 years). The histologic subtype of the PBC included invasive ductal carcinoma in 46 (81%), metaplastic carcinoma in 7 (12%), invasive pleomorphic lobular carcinoma in 3 (5%), and mixed ductal and lobular type in 1 (2%) of 57 cases.

Table 1 Comparison of immunohistochemical results for GATA3 and SOX10 in MBC

GATA3 MBC	SOX10 MBC		
	(+)	(−)	Total
(+)	46% (26)	37% (21)	82% (47)
(−)	12% (7)	5% (3)	18% (10)
Total	58% (33)	42% (24)	P = .49

Most (45/57 [79%]) of the PBC cases were grade 3, the remaining were grade 2. The biomarker status of the PBC was ER+/HER2− in 17 (30%), ER+/HER2+ in 1 (2%), and TNBC in 39 (69%) of 57 cases. Therefore, we observed a biomarker discordance rate of 31% between PBC and MBC, with most discordance due to loss of ER in the metastasis. Most (9/17 [53%]) of the ER-positive PBC cases showed low-level ER expression, with ≤10% staining. Only 1 (2%) of 57 MBC specimens was subjected to decalcification in processing, and it was discordant for ER (the PBC was ER positive with 80% staining). One (2%) of 57 MBC specimens had prolonged cold ischemic time of 71 minutes and was discordant for ER (the PBC was ER positive with 2% staining).

3.1. Expression of GATA3, SOX10, and AR in MBC

Overall, the MBC was 82% GATA3+, 58% SOX10+, and 25% AR+ (Tables 1 and 2). Most GATA3-negative MBC cases were SOX10 positive (7/10 [70%]; Figure), and SOX10 expression seemed independent of GATA3 expression (Table 1). Nearly all MBC cases (95%) were positive for either GATA3 or SOX10, with 46% dual positive and 5% of cases negative for both markers (Table 1). AR expression was observed in 14 (30%) of 46 cases of GATA3-positive MBC, whereas no GATA3-negative MBC expressed AR (Table 2). AR positivity was significantly more frequent in SOX10-negative MBC (11/23 [48%]) versus SOX10-positive MBC (3/33 [9%]; P = .001). AR expression tended to be higher in GATA3-positive MBC (Table 2) and in tumors in which the PBC was non-TNBC (7/19 [38%]) versus TNBC (9/37 [24%]).

Table 2 Comparison of immunohistochemical results for GATA3 and AR in MBC

GATA3 MBC	AR MBC		
	(+)	(−)	Total
(+)	25% (14)	57% (32)	82% (46)
(−)	0% (0)	18% (10)	18% (10)
Total	25% (14)	75% (42)	P = .10

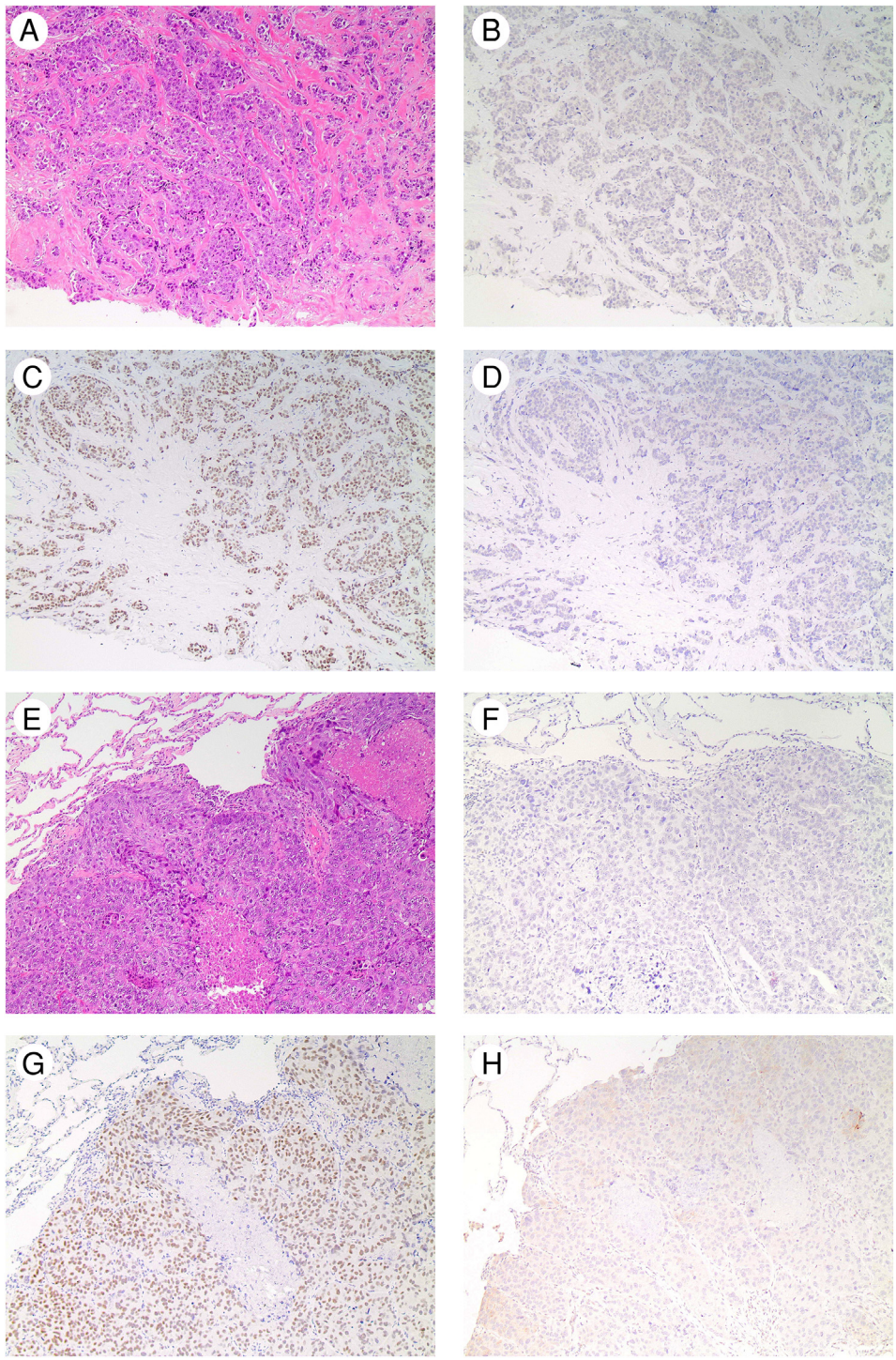

Figure Example case from a 46-year-old woman with grade 3, triple-negative invasive ductal carcinoma, who subsequently developed a lung metastasis after a 3-year interval. A, Photomicrograph of PBC. B, PBC is negative for GATA3. C, PBC is positive for SOX10. D, PBC is negative for AR. E, Photomicrograph of MBC. F, MBC is negative for GATA3. G, MBC is positive for SOX10. H, MBC is negative for AR. A-H, Original magnification ×10.

3.2. Concordance of PBC with MBC

The expression of GATA3, SOX10, and AR in the MBC was compared with their expression in available matched PBC. In the PBC, GATA3 was the most sensitive marker and AR the least. Positive rates for all 3 markers were higher in the PBC compared with MBC. Overall, the PBC was GATA3+ in 37 (84%) of 44, SOX10+ in 27 (63%) of 43, and AR+ in 18 (42%) of 43 cases. Overall concordance between the PBC and the MBC for GATA3, SOX10, and

Table 3 Concordance of immunohistochemical results for GATA3 between PBC and MBC

GATA3 PBC	GATA3 MBC		
	(+)	(−)	Total
(+)	79% (35)	5% (2)	84% (37)
(−)	7% (3)	9% (4)	16% (7)
Total	86% (38)	14% (6)	$\kappa = 0.55$

Table 4 Concordance of immunohistochemical results for SOX10 between PBC and MBC

SOX10 PBC	SOX10 MBC		
	(+)	(−)	Total
(+)	53% (23)	9% (4)	63% (27)
(−)	2% (1)	35% (15)	37% (16)
Total	56% (24)	44% (19)	$\kappa = 0.76$

Table 5 Concordance of immunohistochemical results for AR between PBC and MBC

AR PBC	AR MBC		
	(+)	(−)	Total
(+)	24% (10)	17% (7)	41% (17)
(−)	2% (1)	56% (23)	59% (24)
Total	27% (11)	73% (30)	$\kappa = 0.57$

AR was 39 (89%) of 44 ($\kappa = 0.55$), 38 (88%) of 43 ($\kappa = 0.76$), and 33 (80%) of 41 ($\kappa = 0.57$), respectively (Tables 3-5). Marker discordance between PBC and MBC was caused by both expression losses and gains, with AR and SOX10 showing a relatively greater frequency of expression loss in the metastasis in 41% and 15%, respectively, compared with GATA3 (5%; Tables 3-5). However, GATA3 showed the highest frequency of expression gains in MBC (42%) compared with SOX10 (6%) and AR (4%; Tables 3-5). The frequency of GATA3 expression in the MBC was significantly greater if the PBC was non-TNBC (18/18 [100%]) versus TNBC (29/39 [74%]; $P = .022$). There was a trend toward increased SOX10 expression in the metastasis if the primary tumor was TNBC (26/39 [67%]) versus non-TNBC (7/18 [39%]; $P = .08$). AR showed an inverse trend; AR expression in the MBC was more likely if the PBC was non-TNBC (7/19 [37%]) versus TNBC (9/37 [24%]; $P = .2$).

4. Discussion

In our study, we demonstrate that SOX10 is a sensitive lineage marker for both primary and metastatic TNBC and will label approximately two-thirds of these tumors. Our analysis indicates that SOX10 expression is stable between primary and metastatic lesions, and it showed the highest level of concordance compared with GATA3 and AR. The primary reason that SOX10 is useful is because it is sensitive in the subset of breast cancers (TNBC) in which standard breast lineage marker sensitivity is reduced. Although we note that GATA3 is more sensitive than SOX10 overall, SOX10 is a useful adjunct because it will capture a high percentage of GATA3-negative metastases. Furthermore, GATA3 and SOX10 reactivity seems independent, and these markers are complementary because they preferentially label different subsets of triple-negative MBC (GATA3 in non-TNBC PBC with unstable biomarker expression versus SOX10 in primary TNBC). Compared with SOX10 and GATA3, we found AR to have limited utility as a breast lineage marker due to its low sensitivity. In contrast to SOX10, AR was a poor supplement to GATA3, as it failed to highlight any GATA3-negative MBC.

SOX10 is a transcription factor that plays a role in neural crest cell survival and differentiation [12]. SOX10 expression is seen in normal salivary gland tissue, bronchial cells, and myoepithelial cells of the breast [13]. In surgical pathology, SOX10 IHC is primarily used as a melanoma and nerve sheath marker [13]. In mammary cells, SOX10 activation is associated with expanded stem/progenitor activity and is reported to play a role in epithelial-to-mesenchymal transition [14]. In PBC, SOX10 positivity has been reported in 66% of TNBC and in metaplastic carcinomas, but only in 5% of non-TNBC [15]. To our knowledge, there has been only one prior study of SOX10 expression in MBC. However, their prospective analysis contained relatively few TNBC (n = 8) and was done using tissue microarrays [16]. In their series, SOX10 expression was observed in 38% of triple-negative MBC, versus 0% of non-triple-negative MBC. GATA3 and SOX10 expression was not 100% concordant, leading the authors to conclude that both perform equally well as breast lineage markers [16]. SOX10 expression is seen in primary and metastatic melanoma [17] and other tumors, and therefore, to avoid this diagnostic pitfall, the interpretation of SOX10 should be done in conjunction with other additional markers (eg, cytokeratins).

GATA3 is a transcription factor that plays a role in mammary epithelial cell differentiation [18] and is linked to the ER signaling pathway [19,20]. In surgical pathology, GATA3 is a sensitive marker of both breast and urothelial carcinomas; however, its expression has also been observed in tumor types including salivary gland, gestational trophoblastic, some pancreatic carcinomas, and many others [21,22]. GATA3 has superior sensitivity compared with older, established breast lineage markers such as GCDFP15 and mammaglobin [23], and it is a sensitive marker for identifying MBC [23,24]. However, the main drawback to GATA3 as a breast lineage marker is that its sensitivity is highly correlated with ER status. Although GATA3 positivity in ER-positive PBC ranges from 91% to 100%, it has a comparatively lower sensitivity in TNBC, with most studies reporting the sensitivity of GATA3 between 43% and 66% in these tumors [25,26].

AR is a steroid hormone receptor and nuclear transcription factor that plays a role in normal breast development and mammary cell proliferation [27]. AR is the most widely expressed nuclear hormone receptor in breast cancer, and it is positive in 85% to 95% of ER+ breast cancers, as well in a large number of carcinomas and TNBCs [28,29]. AR has been the focus of recent attention as a potential candidate for therapeutic targeting, particularly for patients with TNBC. Several clinical trials are currently investigating AR antagonists and modulators for patients with TNBC and treatment-refractory ER-positive disease [30,31]. Meanwhile, the significance of AR expression as a prognostic biomarker in TNBC has been controversial, with several reports describing conflicting results [32]. Similar to GATA3, the expression of AR in breast cancer is highly correlated with ER status and tumor subtype, with AR showing higher expression in ER+ and lower-grade tumors [33]. There is significant variability in the reported prevalence of AR in TNBC, possibly related to differences in primary antibody and cutoff used for positivity. A wide range of 6% to 75% positivity rate has been reported, with most positivity rates reported between 25% and 35% for AR in TNBC [34,35]. To date, no studies have compared the utility of AR as a breast lineage marker in TNBC to GATA3 and SOX10. Few publications have addressed the stability and concordance of AR between PBC and matched MBC.

There are several strengths in the design of our study. Our analysis represents the largest series of cases comparing SOX10 expression in PBC and triple-negative MBC. In contrast to other reports in which only a small subset of series of MBC was TNBC [16], our investigation exclusively focused on triple-negative MBC, which is an important diagnostic dilemma and the most relevant clinical scenario. Sampling bias can be marked with tissue microarray–based analyses; we minimized this potential source of bias by performing IHC on whole tissue sections, which often represented half or the entire tumor in the MBC cases. Also, our present work is the only comparative analysis of SOX10 to both GATA3 and AR with regard to marker concordance and stability in MBC.

In summary, we conclude that using both GATA3 and SOX10 is recommended for confirming a breast site of origin in putative breast cancer metastases that lack ER, PR, and HER2 expression, whereas the addition of AR is not useful. In analyzing PBC, SOX10 could be a useful adjunct to support a mammary primary in a poorly differentiated, triple-negative tumor that lacks a recognizable in situ component, and in which the differential diagnosis includes a nonmammary metastasis to the breast. SOX10 is a sensitive and stable lineage marker in TNBC and can be used to support a mammary primary site of origin in metastases from patients with a clinical history of TNBC. In the appropriate clinical context and in conjunction with IHC results such as positive cytokeratin staining, SOX10 can also suggest a mammary primary if a metastatic lesion is triple negative and melanoma has been excluded.

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