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Androgen Receptor Expression Is Usually Maintained in Initial Surgically-Resected Breast Cancer Metastases, But Often Lost in End-stage Metastases Found at Autopsy

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Abstract

Androgen receptor (AR) is expressed in approximately 70% of primary breast carcinomas and is a promising therapeutic target for metastatic breast carcinoma. Here, we examine AR expression in a population of initial surgically-resected metastases and a separate cohort of end-stage metastases harvested at autopsy compared to their matched primary breast carcinomas. Tissue microarrays of matched primary and metastatic breast carcinomas were labeled by immunohistochemistry for AR, ER, PR, and Her2 and classified into the following previously-described categories: luminal (ER/PR+/Her2–), triple negative (ER/PR/Her2–), Her2 (ER/PR–/Her2+), and luminal loss (ER/PR loss from primary to metastasis). In the cohort of surgically-resected metastases (n=16), AR was expressed in 12/16 primaries and maintained in 11/12 corresponding metastases. Of these, 36% showed stronger AR labeling in the metastases and none showed a decrease. In the cohort of metastases harvested at autopsy (n=16), AR was expressed in 11/16 primary carcinomas and maintained in only 5/11 corresponding metastases. Of these, none showed increased AR and 80% showed decreased AR labeling. AR expression is overwhelmingly concordant between matched primary and metastatic breast carcinomas at initial presentation. These findings validate AR as a therapeutic target in metastatic breast carcinoma and suggest that AR may need to be reevaluated in metastases even if the primary is negative. However, similar to ER/PR, AR expression is often decreased with a trend towards complete loss in end-stage metastases, suggesting a shift of AR expression between initial and end-stage metastases. This suggests an opportunity for targeted anti-androgen therapy at an earlier stage of disease progression.

Keywords

Androgen receptor; breast carcinoma; metastasis

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INTRODUCTION

The androgen receptor (AR) is expressed in approximately 70% of primary breast carcinomas (PBCs), (1–3) including those negative for the estrogen receptor (ER), progesterone receptor (PR) and Her2 (“triple negative carcinomas”) (4–7). Androgens and AR are promising therapeutic targets for breast cancer (8), especially for patients with triple negative cancers for whom traditional targeted therapies are unlikely to impact survival. A single study has documented AR expression in some cases of metastatic breast cancer (MBC) (9). However, no prior studies have evaluated AR expression in metastatic breast cancers in relation to their matched PBCs. Here, we examine AR expression in a population of initial surgically-resected metastases as well as in a separate cohort of end-stage metastases harvested at autopsy compared to their respective matched PBCs.

MATERIALS AND METHODS

Tissue microarray construction

This study was approved by the Institutional Review Board of the Johns Hopkins Medical Institutions. Three tissue microarrays (TMAs) were constructed from archived paraffin tissue blocks containing PBCs and surgically-resected matched MBCs from 16 patients (Table 1). Each TMA consisted of 99 spots, each measuring 1.4 mm in diameter. Five to ten spots per PBC and MBC tumor sample were taken to minimize sampling error. In total, these 3 TMAs contained 135 spots of primary tumor from the 16 PBC and 135 spots of metastatic tumor from the 16 matched MBC. In addition, we evaluated a series of previously-described single patient TMAs constructed from paraffin tissue blocks of archived PBCs and from multiple MBCs sampled at rapid autopsies on 16 patients who died of widely metastatic breast carcinoma (Table 2) (10). In brief, all but one autopsies were performed within 4 hours of death, and the metastases harvested from autopsy were formalin-fixed and processed similarly to surgical breast specimens at the Johns Hopkins Hospital. The single patient autopsy TMAs contained four to five spots per metastasis and in total contained 169 spots of PBCs and 895 spots of MBCs derived from 195 different metastases. Non-neoplastic breast tissue harvested at autopsy was available in 8 patients and was included in each respective TMA. The remaining TMAs contained archived non-neoplastic breast tissue from the time of diagnosis of the PBC.

Immunohistochemistry and expression scoring

The TMAs were labeled by immunohistochemistry (IHC) for AR by using the AR (N-20) rabbit polyclonal antibody from Santa Cruz Biotechnology (SC-816) at 1:500 dilution, with detection via LEICA Polyvision+ (PV6119). Briefly, unstained 5- μ m sections were cut from paraffin TMA blocks; slides were de-paraffinized by routine techniques, steamed for 45 min in sodium citrate buffer, cooled for 5 min, blocked with peroxidase blocking solution for 5 min, incubated with the primary antibody for 45 min at room temperature, and incubated with the secondary antibody for 30 min.

The TMAs were also labeled for ER (monoclonal, clone 611, catalogue no. ORG-8871, Predilute, LEICA Microsystems; Bannockburn, IL), PR (monoclonal, clone 16, catalogue no. ORG-8721, Predilute, LEICA Microsystems; Bannockburn, IL), and Her2 (Herceptest kit, Dakocytomation, CA) using standard methods. Briefly, unstained 5- μ m sections were cut from paraffin TMA blocks; slides were de-paraffinized by routine techniques, steamed for 30 min at 90 °C in 1X sodium citrate buffer, cooled for 5 min, then incubated with the primary antibody.

IHC labeling for ER and PR were performed on the Benchmark XT autostainer (Ventana Medical Systems Inc, Tucson, AZ) using I-View detection kit. Fluorescence in situ

hybridization analysis for HER-2 amplification was performed on all cases with 2⁺ (equivocal) IHC results using the Path Vysion kit (Des-Plaines, IL). To qualify as HER-2 positive for this study, a case had to demonstrate either a 3⁺ (strong positive) IHC score or a HER-2 fluorescence in situ hybridization amplification ratio of greater than 4 (11). As previously described (11), we chose the cut-off of 4 (above the current cutoff of 2.2) to avoid cases with low level amplification of Her-2, the significance of which is unclear.

Hormone expression was scored by labeling intensity (none, weak, moderate or strong) and percentage nuclear labeling (0–100%), with any labeling considered a positive result. Her2 expression was scored using established criteria from 0 to 3+ using labeling intensity and proportion of complete membranous staining. The hormone and Her2 expression was scored individually on each TMA spot, and an average of all spots per site was calculated. AR, PR, ER, and Her2 expression were scored separately and blindly of the clinicopathologic patient characteristics and reported ER/PR/Her2 status from the surgical pathology report. The immunohistochemical stains were independently scored by two pathologists. Fisher's Exact Tests were performed to assess statistical significance of the categorical data.

The hormone receptor and Her2 expression was used to classify cases into the following categories: luminal (ER/PR+, Her2–), triple negative (TNC) (ER/PR/Her2–), Her2 (ER/PR–, Her2+), and luminal loss (loss of ER or PR from PBC to MBC) (12).

RESULTS

Cohort of surgically-resected metastases

The clinicopathologic characteristics of patients in the cohort of surgically-resected metastases, "surgical pathology cases (SPC) 1–16," are seen in Table 1. To summarize, 3 patients had invasive lobular carcinoma (SPC 4, 11 and 12) and the remaining 13 had invasive ductal carcinoma. The ages at diagnosis ranged from 33–58 years (average, 44 years). The sites of metastasis were solitary and were brain (n=7), lung (n=5), gastrointestinal tract (n=3), and ovary (n=1). Three patients presented with metastatic disease at the time of initial diagnosis (SPC 1, 3 and 12), and the average time to development of metastasis in the remaining 13 patients was 4.1 years (range 1–7 years, median 4 years). Excluding the 3 patients who presented with metastases at the time of diagnosis, all of the remaining 13 patients received chemotherapy prior to the development of their metastases. The chemotherapeutic agents included adriamycin, cyclophosphamide, taxols and carboplatin. One of the 8 patients with ER+ disease declined hormonal therapy; all of the others received either Tamoxifen or an aromatase inhibitor.

The cohort of surgically-resected metastases was composed of 8 luminal cases (ER/PR+, Her2–), 6 TNC cases (ER/PR/Her2–), 2 Her2 cases (ER/PR–, Her2+), and no luminal loss cases (ER or PR loss from PBC to MBC) (summarized in Table 3). No case was ER+, PR+ and Her2+. The results of the ER, PR and Her2 staining of the PBCs performed on the TMAs were completely concordant with the results of the ER/PR/Her2 staining performed on whole sections at the time of diagnosis and documented in the surgical pathology reports. All 3 primary ILC expressed AR. All luminal and Her2 PBC expressed AR, while 2/6 TNC cases did ($p < 0.01$); in total, 12/16 PBC (75%) showed AR labeling (Table 3). Importantly, then internal control of normal breast tissue was positive for AR in all cases of AR-negative primary tumors. AR expression was maintained in 92% (11/12) of the corresponding MBC. Of these, 36% (4/11) showed stronger AR labeling in the metastasis (Figure 1), and none showed a decrease. The 4 cases with increased AR expression consisted of 2 luminal, 1 Her2 and 1 TNC case. The 1 case with complete AR loss in the MBC had luminal phenotype (SPC 16). In addition, AR expression was gained in 1 of the 4 TNC cases in which the sampled PBC was AR negative (SPC 15, Figure 2). Of note, the MBC of the 3 patients who

presented with metastases (Cases SPC 1, 3, and 12) had identical AR expression as the PBC (Figure 3).

All 4 of the MBC with increased AR expression as compared with the PBC were metastases to the lung, and only 1/5 lung MBC (20%) showed no change in AR expression. This lung MBC was in one of the patients who presented with the metastasis (SPC 2). In contrast, 71% (5/7) of brain MBC, 100% (1/1) of ovarian MBC, and 100% (3/3) of gastrointestinal MBC showed no change in AR expression. The 1 gain of AR and 1 loss of AR in MBC both occurred in brain metastases.

Cohort of metastases harvested at autopsy

The clinicopathologic characteristics of patients in the cohort of metastases harvested at autopsy, “autopsy pathology cases (APC) 1–16,” are seen in Table 2. To summarize, one patient had invasive lobular carcinoma (APC 1) and the remaining 15 had invasive ductal carcinoma. The ages at diagnoses ranged from 28–71 years (average, 47 years), and the ages at death ranged from 37–79 years (average, 53 years). The number of metastatic sites detected per patient at autopsy ranged from 2–18 (average, 11). The mean post-mortem interval of all cases was 3.42 hours. All patients were ultimately refractory to multiple rounds of hormonal therapy and chemotherapy.

The cohort of metastases harvested at autopsy was composed of 5 luminal cases, 5 luminal loss cases, 5 TNC cases, and 1 Her2 case (summarized in Table 3). No case was ER+, PR+ and Her2+. The results of the ER, PR and Her2 staining of the PBCs performed on the TMAs were concordant with the results of the ER/PR/Her2 staining performed on whole sections at the time of diagnosis and documented in the surgical pathology reports. The one primary ILC expressed AR. Similar to the surgically-resected cohort, all luminal and Her2 PBC expressed AR, and 4/5 luminal loss PBC expressed AR, while only 1/5 TNC did ($p < 0.02$). In total, 11/16 PBC (69%) showed AR labeling, which was similar surgically-resected cohort in which 12/16 (75%) PBC were AR positive.

In contrast to the surgically-resected cohort in which AR expression was maintained in 92% of cases, AR expression was maintained in only 45% (5/11) of the corresponding MBC in the autopsy cohort ($p < 0.05$). Of these, 80% (4/5) showed decreased AR in the metastasis ($p < 0.003$), and no cases showed increased AR (Table 3). The 6 cases showing complete loss of AR expression in the MBC included 3 luminal loss cases (Figure 4), 2 luminal cases and 1 Her2 case. AR expression was not gained in any of the 4 cases in which the PBC was AR negative. There was no association between metastatic site and AR expression in this cohort. Androgen receptor expression was present in all 8 cases of normal breast tissue harvested at autopsy, including in 4/4 cases with AR negative metastases.

Five of the cases with decreased or lost AR expression in the MBC also had initial axillary lymph node metastases sampled at the time of initial diagnosis which were also included on the TMAs (APC 3, 7, 11, 14 and 15). In all 5 of these cases, the initial lymph node metastasis had the same AR expression as the PBC. The axillary lymph node metastases sampled at autopsy had the same average AR expression as the other hematogenous MBCs harvested at autopsy.

DISCUSSION

The role of ER and PR in the pathogenesis and treatment of both PBC (13–15) as well as MBC (16) are thoroughly studied. Limited therapeutic options are available for women whose breast cancers do not express ER, PR or Her2. AR expression has been found in approximately 70% of PBCs (1–3), including a subset of those negative for ER, PR and

Her2 (4–7). In particular, increased AR expression has been correlated with apocrine phenotype of in situ and invasive ductal carcinoma (17), lobular carcinoma (18), Her2 positivity (6), and higher grade ductal carcinomas (5).

A phase II clinical trial is ongoing evaluating the efficacy of bicalutamide, a nonsteroidal antiandrogen which binds to AR in target tissues, in patients with advanced AR+/ER-/PR- breast cancer (7). Bicalutamide has shown efficacy in clinical trials for patients with prostate cancer, which characteristically expresses AR (19). However, whether AR expression is retained in MBC of AR-positive PBC or whether conversion to AR positivity can occur has not been well-studied. Schippinger et al., described AR expression in 70% of MBCs, but it not reported whether these metastases represent a first time metastatic event or end-stage events (9). AR expression in MBC has never previously been compared to the expression in the patient's matched PBC.

In this study, we investigated the relationship between AR expression in both initial surgically-resected metastases and end-stage metastases harvested at autopsy as compared to their matched PBCs. This is the first study to compare AR expression in matched PBCs and MBCs. Similar to immunohistochemical scoring criteria for ER and PR (20), we considered any immunolabeling for AR to be a positive result.

Our results show that AR is expressed in 69–75% of PBCs (autopsy and surgical pathology cohorts, respectively), which is consistent with the previously reported values (1–3). AR was seen in all primary ILC and Her2 cases, similar to the trends reported in the literature (6,18). We also confirm that AR expression can also be seen in TNC cases (4), albeit in fewer cases (20–33%) than in luminal cases (100%).

Additionally, our findings indicate that AR expression is overwhelmingly concordant between matched PBC and MBC at initial presentation, with a trend towards increased expression. AR expression was gained in one case. While this may be due to heterogenous AR expression in the primary cancer, this suggests that the AR may need to be reevaluated in MBC, even if the sample of the PBC is negative. The patients who presented with metastatic disease (n = 3) showed the same AR expression in the MBC as in the PBC.

Changes in AR expression showed limited variation with site of metastasis in the cohort of surgically-resected cases. All of the metastases with increased AR expression compared to the PBC were in the lung, but the total case number (n = 4) is small. There was no correlation between AR expression patterns based on site of metastases in the cohort of cases harvested at autopsy.

Notably, in our study AR expression was decreased with a trend towards complete loss in end-stage MBC sampled at autopsy, particularly in the setting of cases showing hormone receptor loss (luminal loss cases). This may reflect selection of hormone receptor negative breast cancer in end-stage, multi-treatment refractory disease in contrast to initial metastases, which reflect resistance to initial first line therapy. One could postulate that the loss of AR labeling seen in some autopsy MBC could be an artifact of the autopsy collection process, e.g., delayed fixation or increased proteolysis (“pre-analytic factors”). However, the presence of strong AR expression in the benign ductal epithelium of the non-neoplastic breast tissue harvested at autopsy, including 4/4 cases with AR negative metastases, serves as an internal control supporting our view that the loss of AR in the metastases is real, and not an effect of post-mortem interval or fixation. Furthermore, the mean post-mortem intervals were in fact *shorter* in the cases of AR-negative metastases (2.95 hours) than in the AR-positive metastases (4.45 hours). Finally, we have shown that other markers (e.g., epithelial cell adhesion molecule) are strongly expressed in these same metastases (21),

proving that the autopsy tissues are highly immunoreactive, similar to surgical pathology specimens.

The significance of the different AR expression patterns between the initial and end-stage metastases is further highlighted by the patients in the autopsy cohort who also had initial lymph node metastases sampled at the time of primary diagnosis. While the end stage metastases harvested at autopsy showed AR loss compared to the PBC, the initial lymph node metastasis showed the same positive AR expression as the PBC. Along these lines, we have found similar differences in expression patterns of other genes, such as the *MYC* proto-oncogene (22), between initial and end-stage metastases.

The limitations of this study include the relatively small sample size (32 total patients), potential for tumor sampling error introduced by the use of TMA, and the inherent subjective nature of immunohistochemical scoring. No cases of apocrine carcinoma were included, and there were no cases of luminal loss phenotype in the cohort of surgically-resected cases. However, the following measures were taken to address these potential limitations. The clinicopathologic characteristics of the patients in the surgical cohort were otherwise similar to those in the autopsy cohort. Five to ten large (1.4mm) spots were taken per tumor site to minimize sampling error, and the immunohistochemical stains were independently scored by two pathologists. Independent review of all histologic tumor grades was performed, and ER, PR and Her2 staining was repeated and re-scored on each tumor on the TMAs, rather than reported from the initial surgical pathology diagnosis.

In conclusion, our findings validate the AR as a therapeutic target in MBC, even in triple negative phenotypes, and suggest a shift of AR expression between initial and end-stage MBC, similar to ER/PR expression. This points to an opportunity for therapy targeting the androgen receptor at an earlier stage in disease progression.

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Figure 1. Androgen Receptor Labeling is Increased in 36% of Initial Surgically-Resected Metastases which Retain Androgen Receptor

Surgical pathology case 13 is an invasive ductal carcinoma with triple negative phenotype which shows increased androgen receptor (AR) labeling from the primary (A, H&E; B, AR immunostain) to the lung metastasis (C, H&E; D, AR immunostain) (x 64).

Figure 2. Androgen Receptor Labeling is Gained in One Case of Initial Surgically-Resected Metastases

Surgical pathology case 15 is an invasive ductal carcinoma with triple negative phenotype which shows gain of androgen receptor labeling from the primary (**A**, H&E; **B**, AR immunostain) to the lung metastasis (**C**, H&E; **D**, AR immunostain) (x 64).

Figure 3. Androgen Receptor Labeling is Maintained with no Change in Patients who Presented with Initial Surgically-Resected Metastases at the Time of Diagnosis

Surgical pathology case 12 is an invasive lobular carcinoma (ILC) with luminal phenotype which shows equivalent, maintained androgen receptor (AR) labeling from the primary (A, H&E; B, AR immunostain) to the gastrointestinal metastasis (C, H&E; D, AR immunostain) (x 64). All cases of ILC exhibited AR expression in the primary carcinoma.

Figure 4. Androgen Receptor Labeling is Lost in 31% of Metastases Harvested at Autopsies
 Autopsy pathology case 5 is an invasive ductal carcinoma with luminal-loss phenotype which shows loss of estrogen receptor and androgen receptor labeling from the primary (A, H&E; B, ER immunostain; C, AR immunostain) to the metastatic sites, which included liver (D, H&E; E, ER immunostain; F, AR immunostain), pleura, colon and bone (H&E $\times 64$; ER, AR $\times 100$).

Table 1

Clinicopathologic Information for the Cohort of Surgically-Resected Metastases (SPC Cases 1–16).

Case	Age at Diagnosis (years)	Stage at Diagnosis	Primary Tumor Type and Grade	Phenotype	Interval to Metastasis (years)	Metastasis Location
SPC 1	33	T3N1M1	IDC, Grade 3	Her2	At presentation	Lung
SPC 2	50	T2N1	IDC, Grade 3	Luminal	6	Lung
SPC 3	34	T2N2M1	IDC, Grade 3	TNC	At presentation	Brain
SPC 4	38	T1cN0	ILC, Grade 2	Luminal	3	Ovary
SPC 5	45	yT1aN1	IDC, Grade 3	Luminal	7	Lung
SPC 6	36	T1cN0	IDC, Grade 2	Her2	4	Brain
SPC 7	39	T2N0	IDC, Grade 3	TNC	4	Brain
SPC 8	53	TXNX	IDC, Grade 3	TNC	1	Brain
SPC 9	38	T1cN0	IDC, Grade 3	TNC	5	Brain
SPC 10	53	T2N2	IDC, Grade 3	Luminal	5	Brain
SPC 11	58	T2N0	ILC, Grade 2	Luminal	7	GI (Bowel)
SPC 12	56	TXNXM1	ILC, Grade 2	Luminal	At presentation	GI (Bowel)
SPC 13	44	T2N0	IDC, Grade 3	TNC	1	Lung
SPC 14	33	yT2N1	IDC, Grade 2	Luminal	2	GI (Pancreas)
SPC 15	57	T1N0	IDC, Grade 3	TNC	6	Lung
SPC 16	36	T1cN0	IDC, Grade 3	Luminal	2	Brain

SPC, surgical pathology case; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; TNC, triple negative carcinoma.

Table 2

Clinicopathologic Information for Cohort of Metastases Resected at Autopsy (APC Cases 1–16).

Case	Age at Diagnosis (years)	Age at Death (years)	Stage at Diagnosis	Primary Tumor Type and Grade	Phenotype	Number of Metastatic Sites at Autopsy
APC 1	54	65	T2N0M0	ILC, Grade 2	Luminal Loss	10
APC 2	33	37	T3N1M0	IDC, Grade 3	TNC	18
APC 3	40	48	T1N1M0	IDC, Grade 2	Luminal Loss	13
APC 4	59	68	T1N0M0	IDC, Grade 2	Luminal	15
APC 5	56	61	T2N1M0	IDC, Grade 2	Luminal Loss	14
APC 6	51	53	T2N0M0	IDC, Grade 3	TNC	15
APC 7	48	54	T2N3M0	IDC, Grade 3	Luminal	6
APC 8	38	43	T2NXMX	IDC, Grade 3	Luminal	13
APC 9	71	79	T2N0MX	IDC, Grade 3	TNC	18
APC 10	57	58	T4N1M1	IDC, Grade 2	Luminal Loss	10
APC 11	28	38	T2N1MX	IDC, Grade 2	Luminal	15
APC 12	33	37	T1N1MX	IDC, Grade 3	TNC	5
APC 13	47	48	T2N1MX	IDC, Grade 3	TNC	9
APC 14	42	47	T3N1M1	IDC, Grade 2	Her2	8
APC 15	44	57	T1N1MX	IDC, Grade 2	Luminal	11
APC 16	43	60	T2N1MX	IDC, Grade 2	Luminal Loss	2

APC, autopsy pathology case; ILC, invasive lobular cancer; IDC, invasive ductal cancer; TNC, triple negative carcinoma.

Androgen Receptor Expression in Primary Breast Carcinomas and Their Paired Metastases.

Table 3

Phenotype	Surgically Resected Cases			Autopsy Harvested Cases		
	Total number	Primary AR positive	Metastasis AR positive	Total number	Primary AR positive	Metastasis AR positive
Luminal	8	8/8	7/8	5	5/5	3/5
Luminal loss	0	0	0	5	4/5	1/5*
Triple negative	6	2/6**	3/6	5	1/5**	1/5
Her2	2	2/2	2/2	1	1/1	0/1
Total	16	12/16	12/16 ^I	16	11/16	5/16 ^{II*}

AR, androgen receptor; PBC; primary breast carcinoma; MBC, metastatic breast carcinoma.

^I 36% of surgically-resected MBC which retained AR showed increased levels of expression

^{II} 80% of autopsy-harvested MBC which retained AR showed decreased levels of expression

* Statistically significant change in AR from PBC to MBC (p<0.05)

** Statistically significantly difference in AR between triple negative and luminal/Her2 cases (p<0.02)