Adenoid cystic carcinomas of the breast have low Topo IIα expression but frequently overexpress EGFR protein without EGFR gene amplification

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Adenoid cystic carcinoma of the breast is a rare subtype of breast cancer with basal-like features. Published studies on breast adenoid cystic carcinoma are limited, resulting in relatively scarce information on the value of predictive tumor markers. We studied 20 primary cases of adenoid cystic carcinoma of the breast for expression of estrogen receptor, progesterone receptor, androgen receptor, epidermal growth factor receptor, HER-2/neu, and topoisomerase IIα using immunohistochemistry and fluorescent in situ hybridization methods. Estrogen and progesterone receptor expression were detected in 1 case each. All tumors were uniformly negative for Her-2/neu expression. Androgen receptor and topoisomerase IIα expression were weakly positive in three cases and 7 cases, respectively. Epidermal growth factor receptor overexpression was detected in 13 cases (65% of all cases). Amplification of TOP2A or HER-2/neu gene was not detected in any of the cases. Our study shows that the majority of adenoid cystic carcinomas of the breast do not overexpress Her-2/neu, topoisomerase IIα, or estrogen receptor, and thus, they are unlikely to respond to therapies targeting these proteins. However, these tumors frequently over-express epidermal growth factor receptor, indicating a potential benefit from anti–epidermal growth factor receptor therapy for patients with advanced adenoid cystic carcinomas of the breast.

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1. Introduction

Adenoid cystic carcinoma (ACC), a salivary gland–like subtype of breast carcinoma, constitutes approximately 0.1%
of all breast carcinomas [1]. The typical immunohistochemical profile for ACC is negative for estrogen receptor (ER), progesterone receptor (PR) and Her-2/neu but is positive for basal cell markers including basal cytokeratins (CK5/6, CK14, or CK17) and/or epidermal growth factor receptor (EGFR), p63, SMA, and C-Kit [2,3].

The paucity of reliable predictive markers for advanced cases of triple negative breast carcinomas including ACC remains as a problem.

EGFR (HER-1) belongs to the ErbB family of receptor tyrosine kinases, and its activation has been implicated in breast cancer cell growth and progression. It stimulates a number of different signaling pathways including Ras/mitogen–activated protein kinase pathway, the phosphoinositide-3-kinase/Akt pathway, and the phospholipase-Cγ/protein kinase C pathway [4]. Anti-EGFR therapies are available for certain tumors which over-express EGFR, such as colorectal carcinoma, glioblastoma, and lung cancer. EGFR expression in breast cancer is common [5], particularly in basal-like breast carcinomas [6], which raises the possibility of using targeted anti-EGFR treatment strategies for breast carcinomas overexpressing this protein [7].

TOP2A gene encodes the enzyme topoisomerase IIα (Topo IIα) that catalyzes the breakage and reunion of double-stranded DNA leading to relaxation of DNA supercoils [8]. It is included in a number of fundamental nuclear processes including DNA replication, transcription, chromosome structure, condensation, and segregation. Topo IIα is a molecular target for anthracyclines and sensitivity to the drugs is related to the TOP2A levels, particularly TOP2A gene amplification.

Patients with ACC characteristically present without axillary lymph nodes metastases, but late visceral metastases are not uncommon, and targeted therapies are not currently considered in such cases due to the paucity of data on predictive molecular characteristics in these tumors. Our study provides additional clinical information in a series of breast ACC and explores novel predictive markers not previously investigated in this tumor type.

2. Materials and methods

2.1. Breast tumor samples and patients data

The study included 20 patients (19 female and one male) diagnosed with primary adenoid cystic carcinoma of the breast. The cases were retrieved from the files of Institute of Oncology (Ljubljana, Slovenia), Thomas Jefferson University Hospital (Philadelphia, PA), Creighton University Medical Center (Omaha, NE), and Clinical Center of the University of Sarajevo (Sarajevo, Bosnia, and Herzegovina). All cases were initially diagnosed at these institutions and confirmed upon the central review. Institutional review board of the Creighton University Medical Center has approved the study.

2.2. Methods

2.2.1. Pathologic assessment

Routinely stained hematoxylin and eosin tumor sections were re-examined (Z.G.), and diagnoses were confirmed. Additional relevant histopathologic parameters recorded included histologic grade, angiolymphatic, and perineural invasion, and the presence of tumor necrosis.

2.2.2. Immunohistochemical assays

Immunohistochemical assays for estrogen receptor α (ER; clone 6F11, Ventana Medical Systems, Inc, Tucson, AZ; ER; clone SP1, Lab Vision, Fremont, CA), progesterone receptor (PR; clone 16, Ventana Medical Systems, Inc; PR; clone PgR636, Dako, Glostrup, Denmark), androgen receptor (AR; Clone AR441, DakoCytomation, Inc, Carpinteria, CA), Topo IIα (Clone Ki-S1, DakoCytomation, Inc), EGFR (DAKO EGFR PharmDX diagnostic kit, DakoCytomation, Inc), Her-2/neu (Clone CB11, Ventana Medical Systems, Inc), and cytokeratin 5/6 (D5/16B4, Dako) expression were performed on the formalin-fixed, paraffin-embedded tissue sections using the commercially available kits and automated staining procedures with 3,3′-diaminobenzidine tetrahydrochloride chromogen. All immunohistochemical stains were performed at the central laboratory (Creighton Medical Laboratories and Creighton University Medical Center).

The tumor was regarded as positive for steroid receptors (ER, PR, and AR) if more than 5% of the cells showed nuclear staining [9,10].

For Topo IIα expression only nuclear staining was considered specific. Immunostaining frequency of the tumor cells was scored on a scale ranging from 0 to 4+: 1+ for 1%-5% positive tumor cells; 2+ for 6%-25%; 3+ for 26%-75%; 4+ for more than 75%) [11,12].

Her-2/neu protein expression results were scored according to the American Society of Clinical Oncology/College of American Pathologists Guideline Recommendations [13]. Briefly, cases showing no membrane immunostaining or staining in less than 10% tumor cells were scored 0; cases with weak and incomplete membrane staining in more than 10% of tumor cells were scored 1+; cases with complete membrane staining that was either nonuniform or weak in intensity but with obvious circumferential distribution in more than 10% of the cells were scored 2+: cases with strong membrane staining in more than 30% tumor cells were scored 3+ [13].

Scoring of EGFR expression was performed according to the manufacturers’ instructions: only membranous staining was considered positive. Weak (1+) intensity is defined as faint and incomplete membrane staining. Moderate (2+) and strong (3+) intensity are both varying degrees of circumferential staining of membranes. For statistical purposes,
staining of 1% or more of cells at any intensity was considered a positive result.

### 2.2.3. Fluorescent in situ hybridization

Fluorescent in-situ hybridization (FISH) was performed in evaluation of *EGFR* and *TOP2A* genes and chromosomes 7 and 17 copy numbers respectively (Abbott Molecular Inc, Des Plaines, IL).

The *TOP2A* and *EGFR* SpectrumOrange signals along with SpectrumGreen centromeres’ signals (CEP 17 and 7), respectively, were enumerated in the predominant tumor cell populations. At least thirty nuclei were scored per sample. A tumor was considered to have amplified *TOP2A* gene if the *TOP2A*/CEP17 ratio was 2.0 or greater, to have deleted *TOP2A* if the ratio was 0.8 or less, and to have normal *TOP2A* if the ratio was between 0.8 and 2.0 [14]. The same criteria were applied for the *EGFR* gene status analysis. Polysomy 7 and 17 were defined as 3 or more CEP signals per cell [15,16]. Stromal cells and normal breast epithelial cells served as an internal control.

### 2.3. Statistical analysis

Nonparametric tests (Mann–Whitney rank-sum test) and χ² tests were applied for testing associations between the variables. For the correlation purposes, nonparametric Spearman’s test was used. Survivors were censored at the last follow-up date, whereas patients died of unrelated disease were censored at the time of death. All statistical tests were 2 sided, and *P* values less than .05 were considered statistically significant. Statistical analysis was done using the Statistical Package for Social Sciences, Version 17.0 (SPPS, Inc, Chicago, IL).

### 3. Results

#### 3.1. Clinical characteristics

Clinicopathologic characteristics of the cohort are summarized in Table 1.

All cases were amenable to surgical resection: 12 patients (60%) were treated by simple mastectomy; 5 (25%), by quadrantectomy; and the remaining 3 patients (15%), by segmentectomy (Table 1). Axillary lymph nodes dissection was performed in 13 patients (65%), sentinel lymph node biopsy in five patients (25%), whereas 2 patients (10%) received no axillary exploration. Patients’ mean age was 60.8 years (range, 43–78 years).

Complete treatment regimes were known for 19 patients. Fifteen (78.9%) of these patients received no adjuvant chemotherapy treatment. Three patients developed metastatic disease, one of which was treated by adjuvant chemotherapy. The chemotherapy regimens included CMF protocol (cyclophosphamide, methotrexate and 5-fluorouracil; 2 patients), and a combination of FEC protocol (5-fluorouracil, epirubicin, and cyclophosphamide) and docetaxel (1 patient). One patient receiving adjuvant chemotherapy (CMF protocol) also received endocrine therapy with tamoxifen because of hormonally dependent contralateral invasive ductal carcinoma that developed 3 years after the initial diagnosis.

Outcome data were available for eighteen patients with a median follow-up of 84 months (range, 1–276 months). During the follow-up period, 4 patients (22.2%) had relapsed of which 2 died of the disease (3 and 7 years after the surgery). The third patient had further progression of the disease 8 years after the diagnosis with lung and bone metastases but was alive at last check up. The fourth patient got symptomatic kidney metastases 5 years after the primary diagnosis. It was surgically removed and the patient was disease-free at last check-up 3 years later. Two patients experienced secondary malignancies (one with contralateral breast carcinoma and another with urinary bladder carcinoma, 3 and 17 years later, respectively). One patient died of unrelated disease 4 years after the diagnosis. Neither axillary lymph node involvement nor local recurrences were observed during the follow-up period. Metastases occurred on average 5.5 years after the initial diagnosis.

### Table 1 Pathologic tumor features and clinical characteristics of a cohort of 20 patients with ACC

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor size</td>
<td></td>
</tr>
<tr>
<td>&lt;2 cm</td>
<td>4 (20%)</td>
</tr>
<tr>
<td>2-5 cm</td>
<td>13 (65%)</td>
</tr>
<tr>
<td>&gt;5 cm</td>
<td>2 (10%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>Histologic grade&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>9 (45%)</td>
</tr>
<tr>
<td>2</td>
<td>8 (40%)</td>
</tr>
<tr>
<td>3</td>
<td>3 (15%)</td>
</tr>
<tr>
<td>Axillary lymph nodes</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>0% (0/18)</td>
</tr>
<tr>
<td>Exploration not performed</td>
<td>2 (10%)</td>
</tr>
<tr>
<td>Local therapy</td>
<td></td>
</tr>
<tr>
<td>Simple mastectomy</td>
<td>9 (45%)</td>
</tr>
<tr>
<td>Mastectomy+RT</td>
<td>3 (15%)</td>
</tr>
<tr>
<td>Quadrantectomy</td>
<td>3 (15%)</td>
</tr>
<tr>
<td>Quadrantectomy+RT</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>Segmentectomy</td>
<td>3 (15%)</td>
</tr>
<tr>
<td>Segmentectomy+RT</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>Adjuvant systemic therapy</td>
<td></td>
</tr>
<tr>
<td>Chemotherapy (CMF)</td>
<td>1 (5.26%)</td>
</tr>
<tr>
<td>Chemotherapy (CMF)+tamoxifen</td>
<td>1 (5.26%)</td>
</tr>
<tr>
<td>Chemotherapy (FEC+docetaxel)</td>
<td>1 (5.26%)</td>
</tr>
<tr>
<td>None</td>
<td>15 (78.9%)</td>
</tr>
<tr>
<td>Not available</td>
<td>1 (5.26%)</td>
</tr>
</tbody>
</table>

Abbreviation: RT, radiotherapy.

<sup>a</sup> According to Kleer et al. [19].
3.2. Histology

All cases exhibited characteristic dual population of the luminal and myoepithelial cells forming three basic patterns: trabecular-tubular, cribriform, and solid [17,18] (Fig. 1A and B). Unequivocal vascular and/or perineural invasion were not evident in any of the studied cases including the four metastatic cases.

Histologic grading of the tumor was performed according to the criteria for ACC of the salivary gland. Briefly, grade I included completely glandular tumors; grade II had less than 30% of solid areas, and grade III had 30% or greater of solid pattern [19]. Accordingly, 9 cases (45%) were graded as grade 1; 8 (40%), as grade 2; whereas 3 (15%), as grade 3. Two of 3 high-grade ACCs fulfilled criteria for solid variant with basaloid features as described by Shin et al [20]. Tumor necrosis was observed in 8 (40%) of 20 cases.

3.3. Pathologic staging

Tumor size data were available for 19 cases (Table 1): 4 cases were pT1c, and 13 cases were pT2; 1 case was pT3, and 1 case was pT4 stage. Axillary lymph node metastases were not detected in any of the cases (0/18).

3.4. Steroid receptors expression status

ER was negative in all but one case which exhibited weak nuclear staining of ER in 70% of the tumor cells (Table 2). All but 1 case were also negative for progesterone receptor (different from the-ER positive case), which showed low and heterogeneous PR expression in 20% of the tumor cells. AR was tested in 16 cases, and only 3 cases exhibited weak nuclear staining in less than 5% of the tumor cells.

3.5. HER-2/neu status

All tumors were negative for Her-2/neu protein expression by immunohistochemistry (score 0); 2 cases were further tested with HER-2/CEP17 FISH and showed no HER-2 gene amplification.
of tumor cells (score 1+, Fig. 1C). The remaining 13 samples with a weak nuclear expression of the protein in less than 5% exhibited the TOP2A showed no nuclear staining of Topo IIα protein. The same case showed a weak nuclear positivity of ER-α protein in a case different from the one with the EGFR protein expression was detected in 13 of 20 cases (2 cases of solid ACC with basaloid features which were in a case different from the one with the EGFR expression[21,36,37,38]. Our study also confirmed that EGFR gene amplification despite the common EGFR protein expression[21,36,37,38]. Our study also confirmed that EGFR gene amplification despite the common EGFR protein expression[21,36,37,38]. Our study also confirmed that EGFR protein was commonly expressed in ACC, and this was not considered as positive result.

### Table 2 Predictive markers evaluation using immunohistochemistry and FISH in adenoid cystic carcinomas of the breast

<table>
<thead>
<tr>
<th>Marker</th>
<th>Proportion of cases (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ER-α</td>
<td>5.8% (1/20)</td>
</tr>
<tr>
<td>Positive</td>
<td></td>
</tr>
<tr>
<td>PR</td>
<td>5.8% (1/20)</td>
</tr>
<tr>
<td>Positive</td>
<td></td>
</tr>
<tr>
<td>AR</td>
<td>0% (0/16)</td>
</tr>
<tr>
<td>Positive</td>
<td></td>
</tr>
<tr>
<td>Her-2/neu protein</td>
<td>0% (0/20)</td>
</tr>
<tr>
<td>Positive</td>
<td></td>
</tr>
<tr>
<td>EGFR protein</td>
<td>65% (13/20)</td>
</tr>
<tr>
<td>Positive (scores 1-3+)</td>
<td></td>
</tr>
<tr>
<td>EGFR gene</td>
<td>5.6% (1/18)</td>
</tr>
<tr>
<td>Deleted</td>
<td>2 cases</td>
</tr>
<tr>
<td>Unsuccessful</td>
<td></td>
</tr>
<tr>
<td>Topoisomerase IIα</td>
<td>35% (7/20)</td>
</tr>
<tr>
<td>Positive</td>
<td></td>
</tr>
<tr>
<td>TOP2A gene</td>
<td>5.6% (1/18)</td>
</tr>
<tr>
<td>Deleted</td>
<td>2 cases</td>
</tr>
<tr>
<td>Unsuccessful</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Note</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>A cutoff value was set at 5% for all three steroid receptors.</td>
</tr>
<tr>
<td>b</td>
<td>Immunohistochemistry.</td>
</tr>
<tr>
<td>c</td>
<td>A proportion of stained cells above 1% at any intensity was considered as positive result.</td>
</tr>
<tr>
<td>d</td>
<td>Fluorescent in situ hybridization.</td>
</tr>
<tr>
<td>e</td>
<td>A scale ranged from 1 to 4 (1, 0%-5% positive tumor cells; 2, 6%-25%; 3, 26%-75%; 4, &gt;75%) [11,12].</td>
</tr>
</tbody>
</table>

### 3.6. TOP2A and EGFR status

Topo IIα protein staining was observed in 7 of 20 cases with a weak nuclear expression of the protein in less than 5% of tumor cells (score 1+, Fig. 1C). The remaining 13 samples showed no nuclear staining of Topo IIα. TOP2A gene FISH analysis was successful in 18 cases. No TOP2A gene amplification was observed in any case but one case exhibited the TOP2A gene deletion (TOP2A/CEP17 ratio 0.71). The same case showed a weak nuclear positivity of Topo IIα protein in less than 5% of the tumor cells. The average TOP2A gene signal number per cell ranged from 1.10 to 2.40 (mean, 2.12).

EGFR protein expression was detected in 13 of 20 cases of which 6 cases strongly overexpressed EGFR (intensity scores 2+ and 3+) (Fig. 1D). FISH analysis revealed no EGFR gene amplification in any of the successfully tested cases (n = 18). On average, there were 1.91 EGFR gene signal numbers per cell (range, 1.30-2.27). A deletion of the EGFR gene (EGFR/CEP7 ratio of 0.70) was seen in one case (with 1+ EGFR protein expression) in a case different from the one with the TOP2A gene deletion. No polysomy of the chromosome 7 or 17 were observed in any of the studied cases. No significant correlation was found between various histopathologic and clinical parameters.

### 4. Discussion

Gene expression profiling and immunohistochemical studies classify ACC as a typical basal-like breast carcinoma, characterized by the lack of steroid receptors and Her-2/neu protein expression[2,3,21]. In general, basal-like carcinoma breast carcinomas are characterized by a poor prognosis, yet ACC had been previously associated with an excellent prognosis [21-27], so although ACCs share some features of basal-like carcinomas, there are important biological differences.

Since the majority of patients in our cohort did not receive adjuvant treatment, the present study provides additional insights into the natural course of ACC. It indicates that, in a proportion of ACC patients, late visceral metastases may develop in the course of the disease (5.5 years on average after surgery) without prior axillary lymph node involvement. Two of the patients in our series developed symptomatic kidney metastases, and in one of them PIK3CA and PTEN gene mutations in both primary and metastatic tumors were previously described [28]. These mutations had been associated with a poor outcome and basal-like breast cancer phenotype [29]. The metastatic rate observed in our series is similar to that observed in a meta-analysis study performed by Sinn et al [30] who analyzed 99 patients with primary breast ACC. In both studies, distant metastases mostly occurred 5 years or later after the initial treatment. This indicates that this type of breast cancer may relapse many years after the initial treatment and that long-term follow-up is necessary for the studies on the natural course of disease [30].

None of our cases had axillary lymph node involvement, a disease characteristic described in previous studies in patients with ACC [31,32]. Our study group also included 2 cases of solid ACC with basaloid features which were in one study noted to have axillary lymph node metastases [20]. Low incidence of axillary lymph node metastases observed in ACC is in accordance with their basal-like breast cancer properties because this has also been a characteristic of typical basal-like breast carcinomas [33]. Our study also included one male patient with ACC which is a rare event with only 4 reported cases [1]. The patient had a 20-mm primary tumor and is without relapse at 6 years of follow-up.

There are limited treatment options for the patients with basal-like breast carcinomas, including ACC [34]. Expression of EGFR (HER-1) is strongly associated with triple negative/basal phenotype in breast cancer [6,23,35,36], leading some investigators to use it as a surrogate for detection of a basal subtype of breast carcinoma [36]. Unlike some triple negative breast carcinomas of no special type and metaplastic breast carcinomas with which ACC shares some immunohistochemical, transcriptomic, and molecular features, ACC harbors no EGFR gene amplification despite the common EGFR protein expression [21,36,37,38]. Our study also confirmed that EGFR protein was commonly expressed in ACC, and this was not caused by EGFR gene amplification. The EGFR staining pattern in our study was similar the one depicted in a recent French study characterized by the intensive staining of basaloid
cells and to a much lesser extent of the luminal cells [38]. In contrast, the prevalence of the EGFR gene amplification in breast carcinomas of no special type is between 6% and 8% [39,40] and associated with increased EGFR protein levels [39,40].

A targeted anti-EGFR therapy has given promising results in the treatment of a subgroup of basal-like breast carcinomas [41]. A study of Hoadley et al demonstrated that basal-like breast carcinoma cell lines tend to be more sensitive to EGFR inhibitors in comparison with luminal cell lines. Moreover, the combination of EGFR inhibitors and carboplatin exhibited pertinent synergistic effects [42].

Another potential target for therapy in breast carcinomas is Topo IIα protein (encoded by the TOP2A gene), an essential component of the cell cycle regulatory enzymes and DNA replication [43]. It is the molecular target of anthracyclines, which bind to this enzyme and induce the accumulation of double-stranded breaks in cellular DNA [44]. TOP2A gene amplification predicts favorable treatment response to anthracycline-based adjuvant chemotherapy, particularly in a subgroup with HER-2/neu amplified breast carcinomas [14,44,45]. Tan et al also indicated that a subgroup of triple negative breast carcinomas also is associated with Topo IIα expression but without gene amplification [46]. We report for the first time that TOP2A amplification is not a feature of ACC since none of the studied cases contained TOP2A gene amplification with only a single case harboring a gene deletion. Moreover, only a third of ACC cases in our series exhibited a weak protein expression and in a small proportion of tumor cells (less than 5%). Therefore, it appears unlikely that the ACC patients would benefit from the anthracycline-based chemotherapy.

Finally, steroid receptors including ER and PR appear to play no role in pathogenesis and prognosis of ACC [3,21,47,48]. Although AR is commonly expressed in breast carcinomas [49,50], our study showed that AR expression is not a characteristic of ACC of the breast. Interestingly, triple-negative breast carcinomas, including some special types of triple-negative carcinomas (metaplastic, medullary), tend to exhibit reduced AR expression in comparison with estrogen-receptor positive breast carcinomas [20,51,52].

In conclusion, our study confirmed that ACC of the breast can be associated with late visceral metastases in a number of cases for which targeted chemotherapy may be necessary. Patients with ACC are unlikely to benefit from anthracycline-based chemotherapy due to low Topo IIα expression, whereas the targeted EGFR therapy may hold a promise due to its frequent over-expression in ACC. However, further exploration of the EGFR receptor status and its downstream effectors (eg, RAS, PIK3CA signaling pathways) is necessary to optimize the targeted EGFR treatment modalities [53].

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References

Adenoid cystic carcinoma of the breast


