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Adenoid Cystic Carcinoma of the Breast: An Oncological Center's Experience

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ABSTRACT

Background: Adenoid cystic carcinoma of the breast (ACCB) is a rare breast malignancy. Despite often being a triple negative tumor, it has a favorable prognosis, with low rates of recurrence and progression. The ideal treatment of ACCB is debatable; thus, the aim of this study was to characterize a population diagnosed with ACCB and to evaluate the treatment outcomes.

Methods: We performed a single-center retrospective analysis of patients with a histological diagnosis of ACCB treated at our dedicated Oncological Center between 1987 and 2020. The patients were identified in collaboration with the Anatomical Pathology Department, which also reviewed the surgical pathology reports.

Results: Thirteen women with a median age of 68 years old were diagnosed with ACCB. The most frequent clinical diagnosis was a breast nodule (n=5); the preoperative image was suggestive of malignancy in nine patients, with seven being diagnosed with a ACCB in the preoperative biopsy. Regarding treatment, nine patients underwent conservative surgery, but three required re-excision. Sentinel lymph node biopsy (SLNB) was performed in seven patients, none revealing metastases; one patient had stage III ACCB and was initially treated with a modified radical mastectomy (MRM); the remaining were stage I (n=7) and II (n=5). Adjuvant radiotherapy was performed in eight patients, and two were initially proposed for chemotherapy but were considered unfit. With a median follow-up of 123 months (16-407), one case of local recurrence and two cases of distant metastasis were identified, one of whom died of disease.

Conclusion: ACCB is a rare tumor with a good prognosis; however, as demonstrated, it can present an aggressive behavior. Conservative surgery and adjuvant radiotherapy are the indicated treatment and SLNB may be omitted in grade 1 tumors.

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INTRODUCTION

Adenoid cystic carcinoma of the breast (ACCB) was first described by Geschickter and Copeland in 1945 and constitutes a rare type of primary breast cancer, accounting for 0.1% of all primary breast malignancies. ACCB is a slow-growing tumor that occurs more frequently in postmenopausal women

aged between 50 and 60 years.[1] Bilateral synchronous carcinoma is rare and the most frequent clinical presentation is a well-defined retroareolar mass or mastalgia, with a small percentage of cases being incidentally detected in screening exams of asymptomatic women. A surgical or percutaneous biopsy is necessary to obtain the diagnosis, as there are no pathognomonic imaging signs that can point to this entity.[1-3] Histologically this tumor is similar to the adenoid cystic carcinoma of the salivary glands and is composed of a dual-cell population of epithelial and myoepithelial-basal cells. Despite having a triple negative phenotype, which is absence of expression of estrogen receptors (ER), progesterone receptors (PR) and HER2 in the immunohistochemical analysis, ACCB constitutes a separate subgroup with a very favorable prognosis, local recurrence rate of 3–18%, low rates of progression, as well as a low mortality rate (7.1%).[1-6] This triple negative phenotype may also help to distinguish cribriform areas of ACCB from invasive cribriform carcinomas which exhibit some morphological similarities but are generally strongly and diffusely immunoreactive for ER and PR. Furthermore, invasive cribriform carcinomas are not composed of a dual cell population (epithelial and myoepithelial), expressing only epithelial markers.

The mainstay of treatment of ACCB has not yet been established due to its rare incidence and indolent behavior, which can be confirmed in the literature, as there are mainly case reports,[7-11] or small series.[2,3,12,13] Regarding histological classification, several scores can be applied. Ro *et al.* suggested a division into 3 prognostic groups, according to architectural and cytological features, namely the proportion of solid and cystic components: grade 1 if there is a predominance of glands and cystic components and absence of solid ones; grade 2 when there are less than 30% of solid components; and grade 3 if there are more than 30% of solid components. According to the authors, the higher the proportion of solid components, the more aggressive the tumor and greater the risk of recurrence and metastases.[14] Additionally, the histologic grade assessed by the Nottingham Score may also be used, with prognostic value, which takes into consideration three factors: tubule formation, nuclear pleomorphism and mitotic activity. Recently, the 2019 World Health Organization classification of breast tumors suggested a division of ACCB into three different histologic subtypes, also with prognostic significance: classic (described as a low-grade neoplasia), solid-basaloid and ACCB with high-grade transformation (both with high grade areas).[15] Most studies suggest an advantage in associating radiotherapy to wide local excision,[16,17] whereas chemotherapy appears to have no benefit and is not recommended, according to ESMO.[18] Typically, ACCB is a low-grade tumor and has a small percentage of nodal involvement at diagnosis (about 5%). Distant metastatic disease at diagnosis is extremely rare.[19-21] When metastases are present, the lung is the most common location, although bone, liver, brain and kidney can also be affected. In such cases, usually there is no axillary involvement.[22] Given the low rate of lymphatic spread and lymph node involvement, the role of sentinel lymph node biopsy (SLNB) is still a matter of debate,[2,3,6,23,24] with a study revealing a similar 10-year relative cumulative survival in patients with unknown nodal status when compared to node negative ones.[6] The same authors also acknowledged the absence of nodal metastases in tumors smaller than 1.4cm in a series of 244 patients and another study of 338 patients reported only two cases of nodal metastases in tumors smaller than 2cm.[21]

Our goal was to characterize the population of patients diagnosed with ACCB in our institution, analyze the histopathological features, observe the instituted treatment and evaluate the oncological outcome. In this paper, we intend to help clarifying the best management of this rare breast malignancy.

METHODS

This is a single-center retrospective analysis of patients with a histological diagnosis of ACCB, treated at IPO-Porto from January 1987 to December 2020. The patients were identified in collaboration with the Anatomical Pathology Department, which also reviewed the surgical pathology reports. This Department used the Nottingham Score for tumor grading, since the 2019 World Health Organization Classification of Breast Tumors had not yet been published. Data on demographics, clinical presentation, treatment and outcome was collected by consulting the patients' medical files.

RESULTS

We obtained a sample of 13 female patients, with a median age of 68 years (43–82) with only one of them being premenopausal (Table 1). None of the patients had a known family history of breast malignancy, and two of them had a prior diagnosis of fibroadenoma.

Five cases presented with a breast nodule (38.5%), four as an abnormal imaging finding in screening exams (30,8%), three complained of mastalgia (23.1%) and one of nipple discharge. There was no difference in the laterality of the tumors, with the upper quadrants being the most frequent location (n = 9) (4 in UOQ, 2 in UQT, 3 in UIT, 1 retroareolar, 2 in OQT and 1 in LOQ). The preoperative imaging findings were suggestive of malignancy in nine patients; none of the 13 patients had a multifocal/multicentric tumor and the median lesion size was 2cm on ultrasound (0.9 – 8cm). A preoperative

biopsy was available in 12 patients, namely eight cases of core needle biopsy (61.5%) and four cases of fine needle aspiration, with the latter performed in the early years (Table 2). A diagnosis of Adenoid Cystic Carcinoma was obtained in seven of these biopsies and information regarding tumor grade and immunohistochemistry was missing in four of them. The remaining were hormone receptor (HR) negative in one case and triple negative in two cases; three tumors were grade 1.

Table 1: Population characteristics.

Patient	Age (years)	Hormonal status	Prior breast lesions	Clinical presentation	Laterality
1	54	Postmenopausal	Yes, Fibroadenoma	Palpable nodule	Left
2	81	Postmenopausal	No	Palpable nodule	Left
3	74	Postmenopausal	No	Palpable nodule	Right
4	75	Postmenopausal	No	Palpable nodule	Right
5	43	Premenopausal	No	Mastalgia	Right
6	68	Postmenopausal	No	Asymptomatic	Right
7	73	Postmenopausal	No	Nipple discharge	Right
8	74	Postmenopausal	No	Mastalgia	Right
9	72	Postmenopausal	Yes, Fibroadenoma	Asymptomatic	Left
10	51	Postmenopausal	No	Asymptomatic	Left
11	61	Postmenopausal	No	Mastalgia	Right
12	55	Postmenopausal	No	Asymptomatic	Left
13	54	Postmenopausal	No	Palpable nodule	Left

Table 2: Characterization of the preoperative biopsy.

Patient	Preoperative Biopsy - Pathology report	Grade	Immunohistochemistry	Institution	Year of diagnosis
1	FNA - No signs of malignancy	NA	NA	IPO-Porto	1987
2	FNA - Suspected of malignancy	NA	NA	IPO-Porto	1999
3	FNA - Adenoid cystic carcinoma	NA	NA	IPO-Porto	2000
4	CNB - Complex proliferative lesion	NA	NA	IPO-Porto	2003
5	NA	NA	NA	External	2003
6	FNA - Adenoid cystic carcinoma	NA	NA	External	2004
7	CNB - DCIS + focal invasive carcinoma	NA	NA	IPO-Porto	2009
8	CNB - Adenoid cystic carcinoma	1	Negative HR	IPO-Porto	2011
9	CNB - Adenoid cystic carcinoma	NA	NA	External	2016
10	CNB - Adenoid cystic carcinoma	1	NA	External	2016
11	CNB - Adenoid cystic carcinoma	1	Triple negative	IPO-Porto	2017
12	CNB - Adenoid cystic carcinoma	NA	Triple negative	External	2017
13	CNB - Atypical sclerosing lesion	NA	NA	External	2018

Institution, Institution where the biopsy was performed; FNA, Fine Needle Aspiration; CNB, Core Needle Biopsy; DCIS, Ductal Carcinoma *In Situ*; NA, Not available / Not applicable; HR, Hormonal Receptors; IPO-Porto, Instituto Português de Oncologia do Porto Francisco Gentil

Table 3: Surgical treatment and tumor characteristics.

Patient	Surgery	Tumor size (cm)	Grade	Synchronous disease	IHC	Re-excision	Final margins (cm)	TNM
1	Lumpectomy	1.7	1	No	Triple negative	MRM	>1	pT1N0M0
2	MRM	7.5	3	No	Triple negative	No	>1	pT4N2M0
3	MRM	1.8	2	No	Positive ER (1-10%) Negative PR Negative HER2	No	>1	pT1N0M0
4	Lumpectomy	1.6	1	No	Positive ER (1-10%) Positive PR (1-10%) Negative HER2	No	0.3	pT1N0M0
5	Lumpectomy	NA	1	No	Negative HR	Yes	NA	pT1N0M0
6	Lumpectomy + SLNB	1.4	2	No	Positive ER (10-20%) Negative PR Negative HER2	No	0.1	pT1N0M0
7	Lumpectomy + SLNB	2.2	1	Carcinoma *in situ*	Triple negative	No	0.1	pT2N0M0
8	Total mastectomy + SLNB	1.9	1	No	Triple negative	No	>1	pT1N0M0
9	Lumpectomy + SLNB	2.5	1	Carcinoma *in situ*	Positive ER (1-10%) Negative PR Negative HER2	Yes	0.3	pT2N0M0
10	Lumpectomy + SLNB	1.6	1	No	Triple negative	No	0.1	pT1N0M0
11	Total mastectomy + SLNB	5.8	1	No	Triple negative	No	>1	pT3N0M0
12	Lumpectomy + SLNB	3	1	No	Triple negative	No	0.2	pT2N0M0
13	Lumpectomy	2.3	2	No	Triple negative	No	0.1	pT2N0M0

IHC, Immunohistochemistry; NA, Not available; MRM, Modified Radical Mastectomy; SLNB, sentinel lymph node biopsy; HR, Hormonal Receptors; ER, Estrogen Receptor; PR, Progesterone Receptor

Regarding treatment, surgical therapy was the first approach in all cases, with nine patients undergoing conservative surgery (69.2%) (Table 3). Mastectomy was chosen in case of unfavorable breast/tumor ratio or in the presence of comorbidities that precluded adjuvant therapy. Modified Radical Mastectomy

(MRM) was performed in confirmed cases of carcinoma before the implementation of sentinel lymph node biopsy at our institution. Since this technique was available, seven patients underwent this procedure, none revealing axillary metastasis. However, one of the cases of MRM revealed 6 metastatic lymph nodes out of 15 isolated ones. As for tumor dimension, the mean was 2.05cm (1.4–7.5cm). Nine cases had a triple negative phenotype or were HR negative (absence of expression of ER and PR), three cases were ER positive/PR negative and one was HR positive (ER positive/PR positive). Regarding tumor grade, nine were grade 1, three were grade 2 and one was grade 3. After the first surgical approach, two patients underwent re-excision and one an MRM. Free surgical margins were obtained in all cases: margins of 0.1cm were accepted in four patients, 0.2 or 0.3cm in three patients and greater than 1cm in the remaining. In this series, there were seven patients with stage I breast cancer (53.8%), five with stage II (38.5%) and one with stage III (7.7%).

Regarding adjuvant therapy, eight patients received radiotherapy, two were proposed for chemotherapy and one received hormone therapy, due to slightly higher ER expression levels. One of the patients proposed for adjuvant chemotherapy completed only one cycle due to febrile neutropenia and the other patient showed stage III ACCB (pT4N2M0) who was later considered unfit due to poor performance status.

With a median follow-up of 123 months (16–407), one case of local recurrence and two cases of distant metastases without local recurrence were identified in the patients with the bigger tumors of our sample, one of whom died of the disease (mortality rate of 7.7%) (Table 4). Regarding the case of local recurrence, it was detected at 186 months of follow-up and consisted of a triple negative multicentric ACCB (pT1N0, grade 1). This recurrence was treated with completion mastectomy and SLNB followed by adjuvant radiotherapy, due to surgical margins of 0.1cm. Currently, the patient is alive with no evidence of the disease. Concerning the first case of metastasis (a grade 3, stage III ACCB at diagnosis), it was detected at 4 months of follow-up in the form of bone metastases. The patient was proposed supportive treatment and died of the disease at 16 months of follow-up. The second case of metastasis (initially a grade 1, stage II ACCB) was diagnosed at 25 months of follow-up as bone and lung metastases. This was managed with antalgic radiotherapy, vertebroplasty of L5 and palliative chemotherapy, with good tolerance and stable disease after an initial partial response under AC (Doxorubicin and Cyclophosphamide, suspended due to toxicity), followed by capecitabine and currently lenvatinib after pulmonary progression.

Table 4. Adjuvant therapy and outcomes

Patient	Adjuvant RT	Adjuvant CH	Adjuvant HT	Local recurrence	Distant metastasis	Survival data	Follow-up (months)
1	No	No	No	No	No	NED	402
2	Yes	No*	No	No	Yes (bone metastasis)	DOD	16
3	No	No	No	No	No	DOC	242
4	Yes	No	No	No	No	NED	212
5	No	No	No	Yes (multicentric ACCB pT1N0)	No	NED	210
6	Yes	No	Yes	No	No	NED	199
7	Yes	Yes (1 cicle)	No	No	No	DOC	141
8	No	No	No	No	No	NED	123
9	Yes	No	No	No	No	NED	63
10	Yes	No	No	No	No	NED	47
11	No	No	No	No	Yes (bone and lung metastases)	AWD	48
12	Yes	No	No	No	No	NED	39
13	Yes	No	No	No	No	NED	31

RT, Radiotherapy; CH, Chemotherapy; HT, Hormone therapy; ACCB, Adenoid Cystic Carcinoma; NED, No evidence of disease; DOD, Dead of disease; DOC, Dead of other cause; AWD, Alive with disease; *Due to poor performance status.

DISCUSSION

The results obtained in our series are in line with those described in the literature. ACCB is a rare tumor (13 diagnosed patients in 33 years in our dedicated Oncological Center) with low malignant potential, rare locoregional recurrence or distant metastases, as opposed to other triple-negative breast cancers or the histologically similar and more aggressive adenoid cystic carcinoma of the salivary glands.[2,19]

ACCB was mainly found in postmenopausal women with a mean age of 68 years old which was slightly superior to the range of 50 to 60 years described in the literature. Patients presented mainly with a breast nodule, but it was mostly in the upper quadrants as opposed to a retroareolar location.[1] In our series, there were 4 ER positive tumors (low expression, mostly 1-10%) and 1 PR positive tumor (low expression, 1-10%). Positivity for ER and PR has also been described in the literature in up to 46% and 36% of cases, respectively.[3,19,25,26] Further analysis found no statistically significant differences in the clinical and histological features of ER/PR positive ACCB when compared to triple negative tumors, suggesting that the positive hormonal receptor status may not affect the prognosis.[3] However, these results from Zhang *et al.* should be viewed with caution, as it was a single-center retrospective study of 14 patients, 8 being HR negative and only the remaining 6 being positive. In our study, none of the HR positive patients had locoregional recurrence or distant metastases. Similarly, at 31 and 212 months of follow-up, our three patients with grade 2 ACCB did not have a worse prognosis as it should have been expected, with two of the three cases of recurrence or metastases affecting grade 1 ACCB patients.

Two of the patients presented with a synchronous *in situ* carcinoma. The synchronous occurrence of an *in situ* or invasive carcinoma of another subtype has been described, and in these cases the prognosis is determined by that of the *in situ* or invasive carcinoma.[21]

Regarding the therapeutical regimen and after the required re-interventions, 8 patients were treated with conservative surgery and 7 of those with adjuvant radiotherapy. The patient submitted to a lumpectomy followed by re-excision without adjuvant radiotherapy was our only case of local recurrence, with our recurrence rate of 7.7% being consistent with that described in the literature (3-18%).[2] However, we should not forget the evidence that adjuvant radiotherapy can decrease local recurrence.[16,17]

Concerning SNLB, some studies support its omission, given the low rate of positive nodes at diagnosis (about 5%),[19] and after progression.[24,25] Our results were similar with only one patient with axillary involvement at diagnosis (7.7%), also corresponding to one of the cases of distant metastasis. However, this was a grade 3 ACCB. The remaining case of distant metastatic disease was node negative at diagnosis. As previously stated, available evidence has reported the absence of nodal metastasis in tumors smaller than 1.4 – 2cm,[6,21] but, despite our only case of nodal involvement happened in a 7.5cm tumor, we found no axillary metastasis in 11 patients that had tumors with a diameter of 1.4cm or greater, with 4 of them being greater than 2cm.

CONCLUSION

Considering ACCB's favorable prognosis, establishing an accurate preoperative diagnosis is central to develop an appropriate treatment planning. Based on the literature and our findings in a dedicated Oncological Center, conservative surgery with free margins and adjuvant radiotherapy are the recommended treatments for ACCB. SLNB's role is yet to be defined, but it seems reasonable to be omitted in grade 1 ACCB. This paper provided additional information on the best treatment of a rare tumor, aimed at preventing futile interventions such as the SLNB that could bear additional morbidity to the patient.

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CONFLICT OF INTEREST

None to declare.

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