

Apocrine breast carcinoma as an extremely rare breast cancer subtype – histopathological characteristics

Marta Maksimiuk¹, Michał P. Budzik², Aleksandra Sobiborowicz¹,
Anna Maria Badowska-Kozakiewicz²

¹Students' Scientific Organization of Cancer Cell Biology, Department of Cancer Prevention, Medical University of Warsaw, Poland

²Department of Cancer Prevention, Medical University of Warsaw, Poland

Apocrine carcinoma (AC) is a distinctive and rare type of malignancy, counted for 0.3–4% of all breast cancer cases. It does not have a particular clinical or radiological features, although it is characterized by the apocrine morphology, estrogen receptor-negative and androgen receptor-positive profile. In the present study, among 1122 patients with breast cancer only 5 of them were diagnosed with apocrine carcinoma (0.4%). All patients were above 50 years old (51–63, mean: 57). Tumor size varied from 1.4 cm to 3.8 cm with a mean size of 2.4 cm, while mean size of all 1122 studied cases counted for 1.9 cm. Two tumors were classified as high-grade (G3), 2 as G2, and 1 as G1. Four tumors out of 5 did not affect lymph nodes (pN0 stage), whereas 1 was classified as pN2 with 9/19 regional lymph nodes affected. This observation was consistent with the whole studied group, in which pN0 stage made up the largest percentage. Presented results suggest that AC is less frequent in premenopausal patients. AC tends to present as invasive malignancy without nodal involvement and is usually characterized by relatively less aggressive biological behavior compared to other histological types of breast cancer. Due to the fact that AC is definitely a rare type of breast cancer, modern medicine has still limited treatment options to offer. Further research needs to be conducted in order to develop target therapies for this carcinoma.

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Introduction

According to estimations performed in 2017 by American Cancer Society, breast cancer (BC) is expected to reach 30% of all new cancers diagnosed among women [1]. Apocrine carcinoma (AC) is one of the rarest histological types of this malignancy, comprising from 0.3% to 4% of all cases [2]. ACs are usually estrogen receptor-negative (ER–), progesterone receptor-negative (PR–), but in 100% of cases androgen receptor-positive (AR+). This observation leads to extensive interest in possible treatment encompassing androgen antagonists [3]. On the other hand, about 30% of AC cases are HER-positive, which enables another treatment possibility with monoclonal antibodies targeting this protein. Consequently, 70% of cases without HER2 expression might

be proposed as a subtype of triple-negative breast cancer (TNBC). However, this connection may be misleading due to the fact that AC is characterized by AR positive expression being unparalleled in TNBC [3, 4].

Aim of the study

The aim of the study was to assess histological grade (G), tumor size (pT), regional lymph node status (pN) and expression of ER, PR and HER2 in apocrine carcinoma of the breast in comparison to other studied types of breast cancer.

Material and methods

The material consisted of 1122 tissue blocks derived from patients suffering from breast cancer. The analyzed material

came from biopsies, excisional biopsies and modified radical mastectomies. Histological and immunohistochemical studies were performed. Apocrine carcinoma was detected in 5 out of 1122 samples. Analyzed samples were fixed in 10% buffered formalin phosphate. After 24-hours fixation, materials were dehydrated and then paraffin blocks were cut into sections 4 µm thick. Preparations stained with hematoxylin and eosin were used for defining type of neoplasm according to WHO classification and grading. Immunohistochemical staining was performed for assessing expression of ER, PR and HER2. Evaluation of these markers was performed as follows: ER and PR were categorized as negative – (0%), low positive – (1–10%); nuclear staining in >10% of tumor cells was considered positive both for ER and PR. HER2 expression was determined using HerceptTest™ (Code: K5204, DAKO, Santa Clara, United States).

Results

Five cases of apocrine carcinoma represented 0.4% of all 1122 studied breast cancer samples. All 5 patients were above 50 years old (51–63; mean: 57). Four tumors out of 5 were detected in the left breast. 2 samples were classified as high grade (G3), 2 as G2, and 1 as G1. Tumor size varied from 1.4 cm to 3.8 cm as follows: 1.4 cm (pT1c), 1.7 cm (pT1c), 2 samples – 2.5 cm (pT2), 3.8 cm (pT2). Mean size was 2.4 cm, whereas mean size of all 1122 studied samples reached 1.9 cm. Four out of 5 studied cancers presented without nodal involvement (pN0), while only 1 was classified as pN2 with metastases in 9/19 lymph nodes. This investigation was in consistency with the whole analyzed group, in which pN0 comprised the largest percentage. Distant metastases (M) were not observed in any of the investigated AC cases. As far as immunohistochemistry is concerned, none of 5 analyzed cases expressed ER or PR. Positive expression of HER2 was detected in only 1 sample, which accounted for 20% of studied AC cases. Detailed data on the examined AC cases are presented in the table I.

Discussion

Breast cancer is the most common malignancy among women worldwide [5]. ER, PR and HER2 are commonly used for diagnosing process and choosing appropriate treatment options for particular types of breast cancer. However, AR detected in 100% of ACs is an emerging potential target for accurate diagnosis and targeted treatment [6].

AC is specific for the group of postmenopausal women [3, 7–9]. This was confirmed in the present study, as the mean age of all diagnosed women was 57 years. Given tumor size, all cases were presented in low stage – none of them reached pT3 stage. Similar results were obtained by Mills et al. (2016) [3] – the majority of tumors were assessed as pT1 or pT2 making up 90% of studied cases – and by Seo et al. (2015) [7] – all lesions were described in the range between 1.2 cm and 2.2 cm. As far as nodal involvement is concerned, the vast majority of analyzed tumors were assessed pN0, as in 4 out of 5 cases regional lymph nodes involvement has not been observed. Interestingly, the opposite results were achieved by Liu et al. (2015) [6] – they described molecular apocrine breast cancer (defined as each BC presenting ER–/PR–/AR+ profile) with tendency to affect more lymph nodes than other studied types of BC. However, so defined apocrine cancer did not exhibit all the histopathological traits that were characteristic of classical ACs. Moreover, they detected a close association between lymph node invasion and expression of gross cystic disease fluid protein 15 (GCDFP15) in AC patients. This molecule is regulated by AR and was proposed as a negative marker for AC patients outcome due to significant correlation with shorter disease-free survival (DFS) and overall survival (OS). Unfortunately, as mentioned above, those results cannot have a strict reference into a histologically defined apocrine carcinoma, because both groups of AC, defined molecularly and histologically, are not completely synonymous.

Some studies describe AC without HER2 expression as triple-negative apocrine carcinoma (TNAC) [9]. In the present study 4 out of 5 ACs presented HER2 negativity. In the study con-

Table I. Detailed histopathological characteristics of analyzed apocrine breast cancer cases

Age	Material	Side	Maximal diameter (cm)	Necrosis	Tumor size (pT)	Regional lymph nodes status (pN)	Regional lymph nodes involved	Metastasis (M)	Tumor stage (TNM)	Grade (G)	ER expression	PR expression	HER expression
60	Postoperative material	Left	2.5	–	2	2	9/19	0	IIIA	2	–	–	2+
63	Postoperative material	Left	1.4	–	1c	0	0/18	0	IB	1	–	–	0
56	Postoperative material	Left	1.7	–	1c	0	0/20	0	IB	2	–	–	0
57	Postoperative material	Left	3.8	+	2	0	0/3	0	IIA	3	–	–	0
51	Postoperative material	Right	2.5	–	2	0	0/16	0	IIA	3	–	–	0

ducted by Meattini et al. (2018) [9], TNAC were characterized by lower Ki-67 index and better survival in comparison to group of non-apocrine triple negative tumors. Their multivariate analysis demonstrated that the only significant factor for OS was the histology of TNAC. On the other hand, Vranic et al. (2010) [10] highlighted the necessity of considering apocrine breast cancers as molecularly diverse group and distinguishing pure apocrine carcinomas and apocrine-like carcinomas. According to their study, pure apocrine carcinomas predominantly belong to either HER2 overexpressing or TNBC groups, whereas apocrine-like carcinomas to luminal phenotype (both A and B). What is more, study results suggested that EGFR expression may be essential for the proper identification of apocrine carcinomas when considering doubtful HER2-positive APC.

Numerous studies have proved the prognostic potential of AR expression in BC and its association with more favorable prognosis. Moreover, several experiments discovered a crosstalk between AR and ER by inhibiting each other's activity [11]. Due to emerging role of AR in BCs, new therapies are consequently implemented. One of them encompasses bicalutamide – a nonsteroidal antiandrogen originally used in the treatment of prostate cancer [12]. The study conducted by Huang et al. (2017) [13] revealed the mechanism responsible for effective treatment with bicalutamide usage. This nonsteroidal antiandrogen was proved to block androgen-stimulated oncogenic AR and Wnt/ β -catenin signaling and as an effect to inhibit the growth of AR+/ER– breast cancer.

Conclusions

AC is a distinctive and rare type of breast cancer. It has a tendency to affect older population of females. Although tumors are usually diagnosed in larger average size, they tend to present without regional lymph nodes involvement. Slightly different results concerning characteristics of BC subgroup might be explained by small groups incorporated into different analysis. Owing to AR positive expression, new therapies are developed for more specific treatment, however further research is still needed to develop target therapies for this malignancy. Associations described in the present study should be investigated further, as the group of patients was small, even though representing a rare histological subtype of breast cancer.

Conflict of interests: none declared

Michał P. Budzik

Medical University of Warsaw
Department of Cancer Prevention
ul. Żwirki i Wigury 81
02-091 Warszawa, Poland
e-mail: michal.budzik@wum.edu.pl

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References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics. *Cancer J Clin.* 2017; 67 (1): 7–30.
2. Sekal M, Znati K, Harmouch T et al. Apocrine carcinoma of the male breast: a case report of an exceptional tumor. *Pan Afr Med J.* 2014; 19: 294.
3. Mills A, Gottlieb CE, Wendroth SM et al. Pure apocrine carcinomas represent a clinicopathologically distinct androgen receptor-positive subset of triple-negative breast cancers. *Am J Surg Pathol.* 2016; 40 (8): 1109–1116.
4. Vranic S, Feldman R, Gatalica Z. Apocrine carcinoma of the breast: a brief update on the molecular features and targetable biomarkers. *Bosn J Basic Med Sci.* 2017; 17 (1): 9–11.
5. Allemani C, Matsuda T, Di Carlo V et al. Global surveillance of trends in cancer survival 2000–14 (CONCORD-3): analysis of individual records for 37 513 025 patients diagnosed with one of 18 cancers from 322 population-based registries in 71 countries. *Lancet.* 2018; 391 (10125): 1023–1075.
6. Liu X, Feng C, Liu J et al. Heat shock protein 27 and gross cystic disease fluid protein 15 play critical roles in molecular apocrine breast cancer. *Tumour Biol.* 2016; 37 (6): 8027–8036.
7. Seo KJ, An YY, Whang IY et al. Sonography of Invasive Apocrine Carcinoma of the Breast in Five Cases. *Korean J Radiol.* 2015; 16 (5): 1006–1011.
8. Dalin MG, Desrichard A, Katabi N et al. Comprehensive molecular characterization of salivary duct carcinoma reveals actionable targets and similarity to apocrine breast cancer. *Clin Cancer Res.* 2016; 22 (18): 4623–4633.
9. Meattini I, Pezzulla D, Saieva C et al. Triple negative apocrine carcinomas as a distinct subtype of triple negative breast cancer: a case-control study. *Clin Breast Cancer.* 2018; 18 (5): e773–e780.
10. Vranic S, Tawfik O, Palazzo J et al. EGFR and HER-2/neu expression in invasive apocrine carcinoma of the breast. *Mod Pathol.* 2010; 23 (5): 644–653.
11. Fioretti FM, Sita-Lumsden A, Bevan CL et al. Revising the role of the androgen receptor in breast cancer. *J Mol Endocrinol.* 2014; 52 (3): R257–R265.
12. Arce-Salinas C, Riesco-Martinez MC, Hanna W et al. Complete response of metastatic androgen receptor-positive breast cancer to bicalutamide: case report and review of the literature. *J Clin Oncol.* 2016; 34 (4): e21–e24.
13. Huang R, Han J, Liang X et al. Androgen receptor expression and bicalutamide antagonize androgen receptor inhibit beta-catenin transcription complex in estrogen receptor-negative breast cancer. *Cell Physiol Biochem.* 2017 43 (6): 2212–2225.