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Adenoid Cystic Carcinoma of the Breast: A Multi-institutional Case Series and Review of Literature

Rachel Dileo[1*], Vinay Edlukudige Keshava[3], Sumukh Arun Kumar[3], Rajesh Thirumaran[4] and Christie Hilton[2]

[1]Allegheny Health Network Internal Medicine Department, Pittsburgh, PA, USA

[2]Allegheny Health Network Cancer Institute, Pittsburgh, PA, USA

[3]Bayhealth Medical Center, Dover, DE, USA

[4]Mercy Catholic Medical Center, Darby, PA, USA

[*]**Corresponding author:** Rachel Dileo, Allegheny Health Network Internal Medicine Department, Pittsburgh, PA, USA.
E-mail: rachel.dileo2@ahn.org

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Abstract

Adenoid cystic carcinoma (ACC) is a rare, indolent tumor of the breast, accounting for approximately 0.1% to 1% of all breast cancers. The most common presenting complaint is a painful breast mass and the mean age at the time of diagnosis is 50-60 years. Despite its "triple negative" status (lacking estrogen receptor, progesterone receptor, and Her2/neu expressions), ACC of the breast has a favorable prognosis, in contrast to its aggressive nature at other anatomical sites. Radiological appearances of ACC are generally non-specific; the diagnosis can be made on fine needle aspiration cytology. Although surgery upfront is the cornerstone in treatment, the optimal adjuvant therapy remains uncertain due to the tumor's low incidence. Limited evidence exists regarding the efficacy of chemotherapy, radiation therapy, and hormonal treatments in the adjuvant setting. In the current state of knowledge, results of breast-conserving treatment with postoperative radiation therapy seem to be equivalent to mastectomy alone. Our case series describes five such cases from three institutions, succinctly outlining the clinical characteristics, diagnostic challenges, and treatment considerations related to ACC of the breast. We also review the current literature and emphasize the need for further large-scale research to enhance understanding and inform clinical decision-making for this rare entity.

Keywords: Adenoid cystic carcinoma; Triple negative breast cancer; Chemotherapy; Radiation; Mastectomy

Introduction

Adenoid cystic carcinoma (ACC) is a rare malignancy of the breast, accounting for approximately 0.1% to 1% of all breast cancers. ACC shares histological features with salivary gland tumors, and other common sites of origin are in the uterine cervix, lungs, skin, kidneys, esophagus, and prostate.

The age distribution is broad, being more commonly diagnosed in the fifth and sixth decades of life. Clinically, it follows an indolent course, and the typical presentation is a painful, sub-areolar breast mass. Histologically, ACC displays a biphasic pattern, characterized by small basaloid cells with a solid cribriform pattern or epithelial cells with a tubular growth pattern. The exact cellular origins of ACC remain elusive, although it is estimated that these tumors arise from the ductal epithelium or myo-epithelium. Radiological appearance of ACC is nonspecific, and the diagnosis can be made by fine needle aspiration biopsy. Despite classically being "triple-negative" [lacking estrogen receptor (ER), progesterone receptor (PR), and Her2/neu expressions], ACC of the breast exhibits a favourable prognosis. Unlike its aggressive behavior at other anatomical sites, ACC of the breast has a low rate of axillary lymph node involvement and distant metastasis. Surgical resection remains the cornerstone treatment, while the optimal adjuvant therapy remains uncertain due to the tumor's rarity. In this article, we present five cases of ACC of the breast from three different institutions, and review the current literature, contributing to our understanding of this intriguing malignancy.

Case Presentation

Case 1: 55-year-old female presented with a mass in her left breast, which was discovered on a routine screening mammogram. It was a 0.7 x 0.4 x 0.5 cm, hypo-echoic, mildly irregular mass at the 11 o'clock position of the left breast, approximately 4 cm away from the nipple. She underwent a biopsy which revealed ACC. The tumor was negative for expression of ER, PR, and Her2/neu. She underwent breast conservation surgery (BCS) with sentinel node biopsy (SLNB). Pathology confirmed the diagnosis of adenoid cystic carcinoma measuring 1.5 cm in size. Ductal carcinoma in situ (DCIS) was not identified. Lymphovascular invasion (LVSI) was present and all margins were negative for tumor involvement. Three sentinel lymph nodes sampled were negative for cancer. The tumor stage was pT1 pN0. Chemotherapy was deferred, and the patient underwent adjuvant radiotherapy.

Case 2: 53-year-old female presented with a history of a painful, palpable mass in the outer quadrant of the right breast for one year. She had a history of lobular carcinoma in situ (LCIS) of the left breast. Mammogram revealed an ill-defined, focal asymmetric mass in the 8-9 o'clock position of the right breast, measuring approximately 2 cm in diameter. Ultrasonogram showed ill-defined areas of hypo-echogenicity with posterior acoustic shadowing measuring at least 12 mm concerning for malignancy. Biopsy of the mass resulted as ACC, being negative for expression of ER, PR, and Her2/neu. Breast MRI demonstrated the lesion in the right breast with surrounding enhancement measuring 5.1 cm in the greatest dimension. She elected to undergo bilateral simple mastectomies in view of lobular carcinoma in situ of her left breast. Final pathology reported 3.5 cm ACC of the right breast, stage pT2 pN0. The patient was offered no further cancer-directed treatment.

Case 3: 59-year-old female presented with a focal asymmetry in the retro areolar right breast with questionable architectural distortion detected on her annual screening mammogram. A diagnostic mammogram revealed two indeterminate right breast masses and right axillary adenopathy. A right breast ultrasonogram demonstrated a heterogeneously hypoechoic mass with an echogenic halo and vascularity measuring 1 x 0.9 x 0.8 at 3 o'clock position in the retro areolar region. At 12 o'clock position, 3 cm from the nipple, there was a subtle hypoechoic mass with peripheral echogenicity and no internal vascularity measuring 0.8 x 0.6 x 0.6 cm. The 2 breast parenchymal masses were biopsied and initially confirmed invasive ductal carcinoma, Nottingham histologic grade 1.

Both masses were negative for expression of ER, PR, and Her2/neu. Given the low grade of the triple negative breast cancer, there was further discussion with pathology regarding concerns for possible adenoid cystic carcinoma. Upon additional review, the diagnosis was confirmed to be ACC. Computerized tomography (CT) of the chest, abdomen, and pelvis, and the bone scan were negative for distant metastasis. Patient underwent right skin sparing mastectomy with breast reconstruction as well as excision of 2 sentinel lymph nodes. Surgical pathology confirmed ACC with the greatest dimension of invasive focus measuring 1.5 cm. LVSI and DCIS were not identified. All margins were negative for tumor involvement. The excised lymph nodes were negative for carcinomatous involvement. The tumor stage was pT1c pN0 cM0. The patient was offered no further cancer-directed treatment.

Case 4: 60-year-old female with a history of adenoid cystic carcinoma of the right breast treated with bilateral mastectomies presented approximately 4 years post-operatively with a painful right chest wall lump. 4 years ago, her final surgical pathology had shown a pT2 pN0 cM0, “triple negative”, right-sided breast ACC, measuring 2.9 cm, with no DCIS. Given concerns for disease recurrence, she underwent a repeat surgical resection. Pathology was reported as two out of three portions of tissue containing ACC within 0.2 mm of the inked margin and the remaining one area of fibro-adipose tissue which was faintly ER positive (1%), but negative for PR and Her2/neu expressions. Patient then completed adjuvant whole breast radiotherapy. CT of the chest, abdomen, and pelvis showed a pulmonary nodule measuring 7 mm. Patient then underwent video-assisted thoracoscopic surgery (VATS) with wedge resection which revealed metastatic ACC measuring 1.1 cm. The resection margins were benign and one, Level 11 lymph node was also benign. Subsequently, she was not offered any additional cancer-directed treatment and continues to be followed actively with periodic examinations and imaging without disease recurrence.

Case 5: A 63-year-old postmenopausal female with a history of left breast invasive ductal carcinoma (6 mm, grade 2, stage IA: pT1bN0M0, hormone receptor-positive, HER2-negative) underwent lumpectomy five years ago, followed by adjuvant radiation therapy and anastrozole treatment. A recent screening mammogram identified a 4 mm focal asymmetry in the right breast, classified as BI-RADS 4. A stereotactic biopsy revealed adenoid cystic carcinoma, grade 1, with estrogen receptor (ER) expression of 10%, progesterone receptor (PR) expression of less than 1%, and insufficient tumor tissue for HER2 testing. The patient underwent a right breast lumpectomy with sentinel lymph node biopsy, which confirmed an 8 mm, grade 1 adenoid cystic carcinoma (ER/PR-negative, HER2: 0; pT1bN0M0). Pathology showed residual tumor within 1 mm of the inked posterior margin, prompting a revision lumpectomy. The patient opted to defer adjuvant radiation therapy and is currently under routine surveillance with regular mammograms.

Discussion

Adenoid cystic carcinoma (ACC) of the breast was first termed “cylindroma” by Billroth in 1856 and was first described by Geschickter in 1945 [1]. It accounts for only 0.1 to 1% of all breast malignancies [2-5]. Large case studies and population-based cohort studies by Arpino et al. and Ghabach et al. have reported similar incidences in their studies. The reported age distribution ranges from 38 to 81 years, with a median age at presentation of 60 years.

Although classically described to present as a sub-areolar mass, this attribute is only observed in 50% of patients. Nipple discharge seems to be a rare symptom although this malignancy has a predilection for a location near the areola. The pain that these patients experience is due to peri-neural invasion which is also the mechanism behind pain in ACC of the salivary glands [6]. Radiologically, the findings are non-specific. The mammographic appearance is a benign-appearing smooth or lobulated mass or an irregular asymmetric mass/density. The sonographic appearance of ACC has been reported as a hypo-echoic or heterogeneous mass with irregular contours [7,8]. The mean size of ACC is noted to be 3 cm (ranging from 0.7 to 12.0 cm). Most cases are macroscopically well-circumscribed. Histologically, the cell of origin of ACC remains controversial. The tumor typically consists of two kinds of cell populations; namely luminal cells (round nuclei and eosinophilic cytoplasm, surrounding true gland lumina containing periodic acid-Schiff-positive neutral mucin) and myoepithelial-basal cells (central oval nuclei and scant cytoplasm, and forming pseudo lumina, which result from intraluminal invaginations of the stroma) [3,6]. Immunohistochemically, myoepithelial-basal cells usually express laminin, fibronectin, basal lamina related proteins, and type IV collagen, whereas the luminal cells express proteins related to cell polarization and epithelial differentiation, including fodrin, E-cadherin, and β-catenin [9]. This preserved cell polarity and segregated cell differentiation is postulated to explain the lack of metastatic capacity of ACC of the breast [6].

Similar to ACCs of the salivary gland, ACCs of the breast are characterized by the t(6;9) (q22-23; p23-24) chromosomal translocation, which generates fusion transcripts involving the oncogene MYB and the transcription factor gene NFIB. Several previous studies have reported that this chromosomal translocation is present in over 90% of ACC cases and is a key ACC oncogenic mechanism [9,10]. ACCs of the breast are graded according to the proportion of solid growth: tumors with either cribriform or tubular trabecular pattern and without solid elements are considered grade I tumors with ≤ 30% of solid growth are classified as grade II, and tumors having more than 30% solid growth are designated grade III [2,11,12]. In contrast to what might be expected with triple-negative breast cancers, the majority of cases of breast-ACC rarely involve regional lymph nodes and are associated with excellent survival.

At the time of diagnosis, metastasis to the lymph nodes is a rare finding. Studies have reported the incidence of lymph node involvement at the time of diagnosis to be anywhere between 1.7% and 5.1% [4,5,12]. The majority of the patients have tumors confined to the breast [13-15]. While breast conservation surgery with sentinel node biopsy seems to be the standard-of-care surgery for most invasive carcinomas found at an early stage, the indolent nature of ACC may allow the surgeon to perform a surgical resection of the primary tumor without lymph node sampling. The incidence of lymph node positivity increases with the size of the tumor. Thompson et al. [12]. noted that with such a low incidence of positive lymph nodes in T1-T2 tumors, one must question the need for sentinel lymph node mapping and biopsy if coupled with a clinically negative axillary involvement. A consensus for the treatment of ACC of the breast has not been reached and much of it is owed to the rarity of this malignancy. Options range from a simple local excision to radical mastectomy [4,6,16,17]. The role of radiotherapy following breast conservation surgery remains unclear. Arpino et al [3] reported 14 of 182 patients in their study experienced a local recurrence. Of the 14 patients who recurred, only 3 patients (22%) received adjuvant radiation therapy, while the other 11 patients (78%) did not. The authors hence concluded that post-operative radiotherapy may have a role in the treatment of ACC; similar to DCIS and its invasive counterpart. Neither adjuvant chemotherapy nor hormonal manipulation has been shown to be beneficial in patients with ACC of the breast.

Conclusion

ACC of the breast is a rare tumor with an indolent course, often presenting with breast pain and rarely involving axillary lymph nodes. Despite its triple negative receptor phenotype, breast ACC has more favorable prognosis and outcome, loosely comparable to DCIS of the breast. Surgical treatment entails addressing the breast lesion and sparing the axilla in many cases, as recommended for DCIS. Although adjuvant chemotherapy or hormone therapies have not been shown to be beneficial, a targeted therapy approach towards the fusion transcript of the MYB-NFIB oncogenes also seems promising. Larger population-based studies, coupled with likely machine-based learning models might be the way of the future in establishing the appropriate treatment paradigm for this rare tumor.

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