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Case Report

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Apocrine Carcinoma of the Breast: A Case Report and Review of the Literature

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ABSTRACT

Background: Apocrine carcinoma of the breast is a rare and distinct subtype of invasive ductal carcinoma characterized histologically by large tumor cells with abundant eosinophilic granular cytoplasm and prominent nucleoli. Accurate diagnosis and immunohistochemical profiling are essential for distinguishing this entity from other breast cancer subtypes. Emerging evidence suggests a potential therapeutic role for Androgen Receptor (AR)-targeted treatments in managing this disease.

Case Presentation: The patient was a 55-year-old woman with no significant past medical history who presented for a routine physical examination. A screening mammogram revealed a 1.2 × 0.8 × 0.6 cm superficial mass in the upper outer quadrant of the right breast, along with scattered coarse microcalcifications. A core needle biopsy was performed, and histopathological analysis confirmed the diagnosis of apocrine carcinoma of the breast, a rare subtype of invasive ductal carcinoma. Immunohistochemistry (IHC) demonstrated strong Androgen Receptor (AR) positivity and negativity for Estrogen Receptor (ER), Progesterone Receptor (PR), and HER2. The patient subsequently underwent surgical excision of the tumor. Postoperative recovery was uneventful, and the patient is currently under close clinical follow-up with consideration for AR-targeted therapy in the context of receptor status.

Conclusions: Through a review of the current literature, we highlight the key histopathological, molecular, and clinical features of apocrine breast carcinoma. This case study underscores the importance of accurate diagnosis and comprehensive immunohistochemical analysis in guiding effective treatment strategies. The consistent expression of AR in these tumors supports further exploration of AR-targeted therapies as a promising treatment avenue.

Keywords: Apocrine; Breast; Carcinoma; Androgen; Receptors

INTRODUCTION

Apocrine carcinoma of the breast is a rare and distinct histological subtype of invasive ductal carcinoma that accounts for less than 1% of all breast cancers. It is characterized by large tumor cells with abundant eosinophilic, granular cytoplasm; large round to oval nuclei, and prominent nucleoli. A hallmark of apocrine differentiation is the occurrence of decapitation secretion, although this feature may not always be prominent. Histologically, apocrine carcinomas may exhibit

solid, tubular, or papillary growth patterns and are often accompanied by a desmoplastic stromal response. High mitotic activity, nuclear atypia, areas of necrosis, and calcification can also be observed. Immunohistochemically, these tumors typically demonstrate strong diffuse Androgen Receptor (AR) positivity, as well as expression of Gross Cystic Disease Fluid Protein-15 (GCDFP-15), supporting apocrine differentiation. These patients are usually negative for Estrogen Receptor (ER) and Progesterone Receptor (PR), while HER2 expression is variable and may influence treatment strategies.

The diagnosis can be challenging due to morphological overlap with other rare neoplasms, such as oncocytic carcinomas, more common subtypes, such as Invasive Ductal Carcinoma-Not Otherwise Specified (IDC-NOS) and Invasive Lobular Carcinoma (ILC) [1]. Accurate diagnosis is essential for guiding treatment, particularly given the emerging role of AR-targeted therapies in AR-positive, triple-negative breast cancers.

Here, we present a case of apocrine carcinoma of the breast confirmed by histopathology and immunohistochemical profiling to contribute to the limited literature and highlight the diagnostic and therapeutic considerations associated with this rare entity.

CASE PRESENTATION

A 55-year-old female patient presented to her primary care physician for a routine physical examination with no reported breast symptoms. As part of standard screening, a mammogram of the right breast was performed, revealing a superficial mass measuring 1.2 × 0.8 × 0.6 cm located in the upper outer quadrant. Additionally, scattered clustered coarse microcalcifications were noted throughout the right breast parenchyma, raising suspicion for a neoplastic process. The patient was referred for a core needle biopsy of the lesion for histopathological evaluation.

The tissue specimens obtained consisted of multiple cores of pink-tan soft tissue measuring up to 1.4 × 0.2 cm in aggregate. Microscopic examination demonstrated sheets of infiltrating large tumor cells arranged in solid nests and clusters. The tumor cells exhibited abundant eosinophilic, finely granular cytoplasm, large centrally located nuclei, and prominent nucleoli-features characteristic of apocrine differentiation (Figure 1). No features suggestive of invasive lobular carcinoma or other specific subtypes were observed.

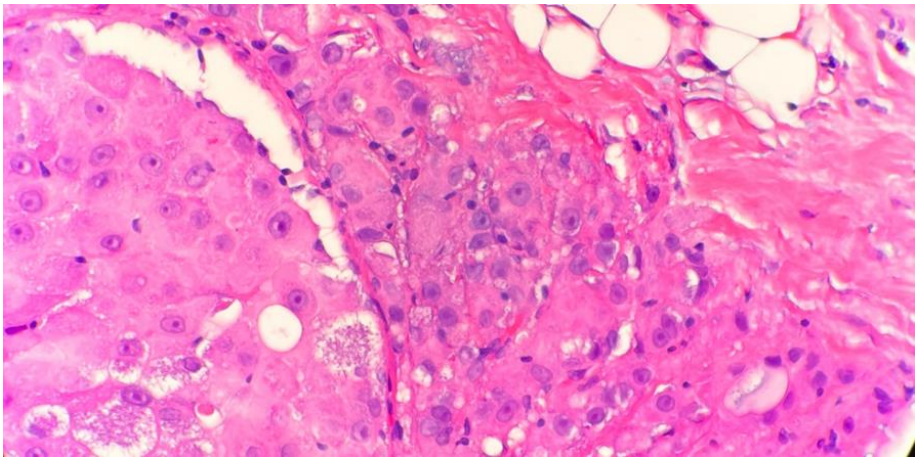

Figure 1: Microscopic examination revealing sheets of infiltrating large tumor cells with abundant eosinophilic granular cytoplasm and prominent nucleoli (H&E 40x).

Immunohistochemical analysis was performed to further classify the tumors. The neoplastic cells showed strong and diffuse nuclear positivity for the Androgen Receptor (AR) (Figure 2). In contrast, the tumor was negative for Estrogen Receptor (ER), Progesterone Receptor (PR), and HER2, confirming a triple-negative but AR-positive immunoprofile-an immunophenotype frequently associated with apocrine carcinoma of the breast. HER2 negativity was determined according to the ASCO/CAP 2018 criteria. More than 95% of tumor demonstrated apocrine features, and the mitotic index was approximately 15%. GCDFP-15 staining showed intermediate intensity in about 50% of tumor cells. Cytokeratin and myoepithelial markers were not performed, as they were not necessary. Following diagnosis, the patient underwent surgical excision of the tumor. The surgical procedure was uneventful, and the patient recovered without complications. Final pathology confirmed clear surgical margins, and there was no evidence of lymphovascular invasion and distant organ metastases. A sentinel

lymph node biopsy was not performed. The patient subsequently continued clinical follow-up at another hospital. Given the tumor's AR-positive status, the patient is currently under close clinical follow-up with consideration for adjuvant AR-targeted therapy, in accordance with emerging treatment approaches for AR-positive triple-negative breast cancer. Ongoing surveillance is planned as part of her long-term management strategy.

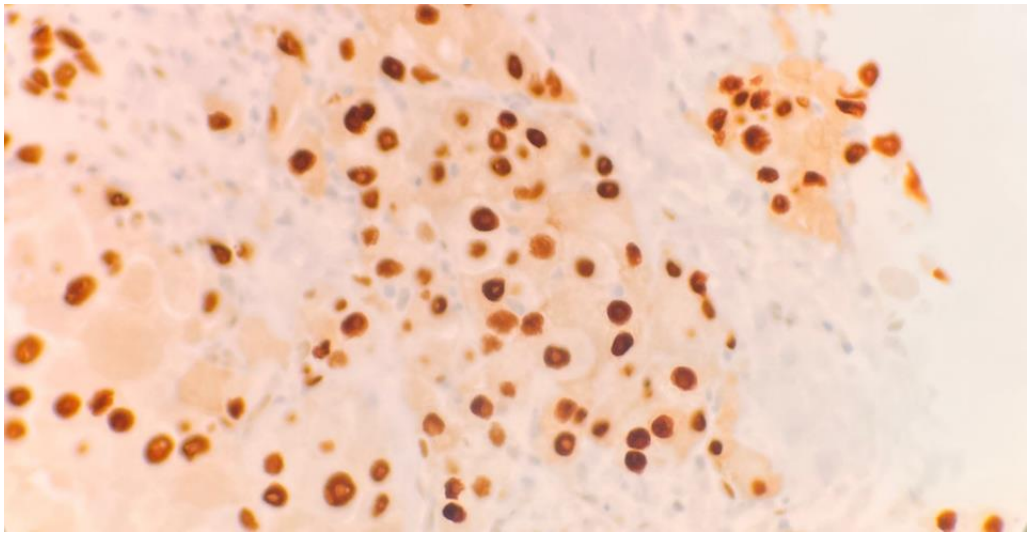

Figure 2: Tumor cells exhibit strong diffuse positivity for the Androgen Receptor (AR) (IHC 40x).

DISCUSSION

Apocrine carcinoma of the breast presents with infiltrating tumor cells displaying apocrine morphology: abundant eosinophilic and granular cytoplasm, well-defined cell borders, enlarged round nuclei, and prominent nucleoli. This apocrine appearance is typically present in more than 90% of tumor cells. These tumors are usually high-grade or poorly differentiated and are frequently associated with Ductal Carcinoma *In Situ* (DCIS), which exhibits apocrine features. Cytologically, they manifest as sheets, clusters, or single cells with abundant eosinophilic cytoplasm; large nucleoli showing variable pleomorphism; and often prominent multinucleation.

Clinically, apocrine carcinomas may present as palpable masses or abnormalities detected via mammography. They are firm with distinct boundaries from surrounding tissue and often appear tan to yellowish due to their lipid content. Histologically, these tumors exhibit solid growth patterns with sheets of tumor cells, tubular formations resembling gland-like structures, or papillary configurations with fibrovascular cores. A desmoplastic stromal reaction characterized by dense fibrous tissue, sometimes accompanied by an inflammatory response with lymphocytes and plasma cells, is common.

Molecularly, apocrine carcinoma of the breast is distinct from other types of breast cancer. It is characterized by Androgen Receptor (AR) positivity and typically lacks Estrogen Receptor (ER) and Progesterone Receptor (PR) expression. Some tumors demonstrate HER2 overexpression or amplification. Mutations in the PIK3CA gene that activate the PI3K/AKT pathway have been observed, suggesting the potential of treatment with PI3K pathway inhibitors [2].

Moreover, apocrine carcinomas may harbor TP53 mutations, which contribute to genomic instability, as well as BRCA1 or BRCA2 mutations, linking them to hereditary breast cancer syndromes and influencing treatment decisions such as those related to the use of PARP inhibitors. Changes in DNA methylation and histone modification patterns impact gene expression and tumor progression [3]. The presence of gross cystic disease fluid protein-15 (GCDFP-15) serves as a marker of apocrine differentiation while EGFR protein expression is common [4].

CK5/6 are variably expressed and can aid in the differential diagnosis of apocrine carcinoma from other triple-negative breast cancers. Elevated Ki-67 indices reflect aggressive tumor behavior. Activation of survival pathways, such as the PI3K/AKT and AR signaling pathways, contributes to the growth and maintenance of tumor cells.

A hallmark of apocrine differentiation is the occurrence of decapitation secretion, where the apical portion of the cell is pinched off into the

glandular lumen, although this feature is not always prominent. In some cases, tumor cells may have a histiocytoid appearance with abundant foamy cytoplasm [5].

Apocrine carcinoma of the breast shares histological features with other breast cancers such as invasive ductal carcinoma, complicating differentiation based on morphology alone. While typically expressing AR and GCDFP-15, not all patients are positive for these markers. Moreover, the absence of ER and PR expression distinguishes apocrine carcinoma from other types of cancer, although this similarity with Triple-Negative Breast Cancer (TNBC) lacking ER, PR, and HER2 expression can lead to diagnostic complexity.

Differential diagnosis between apocrine carcinoma and other breast tumors with similar morphologies is crucial for accurate classification and treatment [6]. Invasive breast carcinoma with focal apocrine differentiation, is a type of invasive ductal carcinoma of No Special Type (NST) that shows some areas resembling apocrine sweat gland cells, with up to 60% of such carcinomas exhibiting these features. However, to be classified specifically as having apocrine differentiation, more than 90% of the tumors must exhibit this morphology. Invasive breast carcinoma, (NST) with an oncocytic carcinoma pattern, displays tumor cells with abundant eosinophilic and granular cytoplasm, well-defined borders, round centrally located nuclei and prominent nucleoli. These tumors are often estrogen receptor (ER)-positive and may show specific chromosomal gains at 11q13.1-q13.2 and 19p13. Granular cell tumors are rare and consist of large, round to polygonal cells with eosinophilic and granular cytoplasm and small central hyperchromatic nuclei; they typically test positive for S100 and CD68 markers but not for keratins. Apocrine Ductal Carcinoma *In Situ* (DCIS) is a form of DCIS with apocrine cytology characterized by the presence of a myoepithelial cell layer around the ducts. Apocrine DCIS shares many features with invasive apocrine carcinoma, including positivity for CK7, AR, and GCDFP-15, and negativity for ER/PR and S100. The critical distinguishing feature is the presence of an intact myoepithelial cell layer, demonstrated by positive staining for myoepithelial markers (such as p63, calponin, or SMA) around the ducts. This myoepithelial presence confirms the *in-situ* nature of the lesion, in contrast to the absence of these markers in invasive apocrine carcinoma.

Apocrine adenosis or atypical apocrine adenosis involves a lobulocentric proliferation of cells with apocrine features, often distorted by stromal fibrosis or sclerosis, also characterized by the presence of a myoepithelial cell layer. Histiocytoid carcinoma frequently shows positive staining for both S100 and CD68, which are generally negative in apocrine carcinoma. This profile reflects its resemblance to histiocytes and helps distinguish it from apocrine and oncocytic carcinomas. Like the others, it is CK7-positive, and as an invasive carcinoma, it lacks myoepithelial markers. E-cadherin is often negative, supporting a lobular phenotype. AR and GCDFP-15 may be variably expressed, but they are less consistent than in apocrine carcinoma. Oncocytic carcinoma can overlap morphologically with apocrine carcinoma due to its abundant eosinophilic cytoplasm, but immunohistochemically it shows distinct features. Like apocrine carcinoma, it expresses CK7 and may also be AR-positive. However, a key distinction is that oncocytic carcinoma often shows positive staining for S100, and is characteristically strongly positive for mitochondrial markers (such as anti-mitochondrial antibody), reflecting the dense mitochondrial content of the cells. It is CD68-negative and, like apocrine carcinoma, lacks myoepithelial markers if invasive. ER/PR expression is more variable and may be positive.

Surgery remains the primary treatment for early-stage apocrine carcinoma of the breast, and the choice between lumpectomy and mastectomy is based on the by tumor size, location, and patient preference. Successful tumor removal is correlated with improved outcomes depending on the disease stage. Following lumpectomy, radiation therapy is typically recommended to reduce the risk of local recurrence. Postmastectomy may also be considered for patients with high-risk features such as large tumor size or lymph node involvement, improving overall survival, particularly in early-stage disease.

Chemotherapy plays a crucial role, particularly in treating higher-grade or advanced-stage apocrine carcinomas, utilizing standard regimens such as anthracyclines, taxanes, and platinum-based agents to reduce recurrence risk and increase survival, especially in node-positive or high-risk patients [7].

AR-targeted therapies, such as bicalutamide or enzalutamide, are promising options due to the high AR expression in apocrine carcinoma of the breast and are especially beneficial in AR-positive, ER-negative tumors. Hormonal therapies such as tamoxifen are generally ineffective due to the usual ER and PR negativity in these cancers [8].

AR antagonists bicalutamide and enzalutamide are widely researched and have been shown to be effective. Their effectiveness was even higher in combination with other drugs, e.g., EGFR inhibitor, PDFGR-beta inhibitor, Erk1/2 inhibitor, PI3K inhibitors, mTOR inhibitors, PARP1 inhibitors,

CDK4/6 inhibitors, BET inhibitors [9]. The outcome of AR-positive tumors was similar between those underwent both radiotherapy and chemotherapy and those underwent chemotherapy alone, but the outcome was superior for patients undergone radiotherapy and chemotherapy in non- AR-positive Breast Cancer subgroup [10].

AR positivity should be incorporated into discussions during multidisciplinary tumor board meetings, and patients who require systemic therapy should be considered for enrollment in clinical trials evaluating AR inhibition or targeted combinations therapies.

Clinical guidelines should emphasize routine AR testing and the inclusion of GCDFP-15 in diagnostic panels to confirm apocrine differentiation. Regular multidisciplinary approach tumor board reviews are crucial for individualized treatment planning and comprehensive management of apocrine breast carcinoma. Further research involving regular tumor board meetings is essential for tailored treatment planning and comprehensive management of apocrine carcinoma of the breast. AR signaling pathways and their regulatory mechanisms is essential for advancing therapy [11].

LIMITATIONS

A notable limitation of this report is the absence of comprehensive molecular profiling, including targeted Next-Generation Sequencing (NGS) and assessment of Homologous Recombination Deficiency (HRD). Given the increasing therapeutic relevance of PIK3CA mutations and BRCA1/2 alterations-both of which can inform the use of PI3K inhibitors or PARP inhibitors, respectively-lack of such profiling limits the ability to fully characterize the tumor's actionable genomic landscape. In particular, targeted NGS covering PIK3CA, TP53, AKT1, PTEN, and BRCA1/2, along with HRD scoring, could have provided critical information for adjuvant systemic therapy selection and clinical trial eligibility. The omission of these data reflects a broader challenge in integrating molecular diagnostics into routine evaluation of rare breast cancer subtypes and underscores the importance of incorporating such testing in future cases where tissue availability permits.

CONCLUSION

In conclusion, diagnosing apocrine carcinoma of the breast remains challenging due to its histological similarities with other breast cancers. Immunohistochemical markers such as AR and GCDFP-15 are crucial for accurate identification. Prognosis and treatment decisions are significantly influenced by hormone receptor status (AR positivity, ER/PR negativity) and HER2 status.

Current treatment strategies include surgery, radiation, chemotherapy, and targeted therapies, particularly AR inhibitors and HER2-targeted agents, which have shown promise in improving outcomes for specific molecular subtypes. Comprehensive immunohistochemical profiling and multidisciplinary team involvement are essential for managing this unique breast cancer subtype effectively.

Ongoing research has focused on novel therapies such as AR inhibitors and immunotherapies, aiming to further optimize treatment approaches. Future studies should prioritize clinical trials to explore new therapeutic targets and refine treatment protocols, ultimately aiming to improve patient outcomes in patients with apocrine carcinoma of the breast.

DECLARATIONS

Competing interests

Not applicable.

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Author contributions

S.D, P.X and K.T. wrote the main manuscript text. P.X. prepared Figures 1-2. All the authors reviewed the manuscript.

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Consent for publication

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Availability of data and materials availability

Not applicable.

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