Surgical and Experimental Pathology

REVIEW Open Access

Apocrine lesions of breast and invasive carcinoma with apocrine differentiation: a brief review

Saba Anjum[1*], Mehwish Mooghal[2], Abdul Rehman[3], Yusra Sellal[1] and Lubna Vohra[2]

Summary
Apocrine metaplastic change is a frequent change in breast pathology. Invasive carcinoma with apocrine differentiation of the breast has unconventional histology, immunohistochemical (IHC), and molecular profile. It has an Estrogen receptor (ER)/Progesterone receptor (PR) negative and an Androgen receptor (AR) positive profile. About 1/3 of cases can show Her2neu amplification through IHC or Fluorescence in situ hybridization (FISH). Lymphovascular invasion (LVI) and lymph node metastasis (LNM) are frequently observed and they often have poor pathological response to chemotherapy. Histologically and molecularly defined apocrine subtypes of breast cancer, although have considerable overlap, yet are different and discrete entities. The decision on using chemotherapy and targeted regimens in these lesions is still controversial which calls for more insight. This could be achieved by acquiring a standardized diagnostic practice, further research, and discussion.

Keywords Breast cancer, Special subtypes, Apocrine carcinoma, Androgen receptor

Introduction

One of the primary causes of cancer among women globally is breast cancer. It holds a high mortality rate, being 2nd to lung cancer (Vranic and Gatalica 2022; Giaquinto et al. 2022). Multiple histologic and molecular genetic types have been included in this diverse and complicated group of disorders. Nearly 70% of all breast cancers are invasive breast carcinomas of no specific type (IBC-NST), while the rest of the 30% constitute various uncommon subtypes, having unique morphology, molecular manifestations, and genetic characteristics. Each subgroup has a distinct clinical course and so are the treatment options (Alencar NNd, Souza DAd, Lourenço and Silva 2022). To enhance diagnostic accuracy and uniformity in reporting, we will briefly review various apocrine lesions of the breast, highlight breast carcinoma with apocrine differentiation, summarize recent research, and identify areas that have potential scope for more exploration.

*Correspondence:
Saba Anjum
saba.anjum@aku.edu
[1]Pathology – Section of Histopathology, Aga Khan University Hospital, Karachi, Pakistan
[2]Breast surgery department, Aga Khan University Hospital, Karachi, Pakistan
[3]National health service, Glasgow, Scotland

Discussion

Apocrine metaplasia

One of the most frequent changes in breast disease is apocrine metaplasia which is a benign non-cancerous condition. It is characterized by the replacement of normal glandular cells by apocrine sweat gland cells which have a distinct appearance when viewed under a microscope. Microscopically, these cells appear large, have abundant eosinophilic cytoplasm with enlarged and prominent nucleoli, mostly seen lining the ducts (Quinn et al. 2022; Abbasi et al. 2019).

Although apocrine metaplastic change in the breast can be easily recognized, however, various immunohistochemical (IHC) markers, such as Epithelial membrane antigen (EMA), Androgen receptor (AR), and Gross cystic disease fluid protein 15 (GCDFP15) can further highlight the change. Moreover, Apocrine cells are also negative for ER / PR receptors and can have varied Her-2neu expression (Quinn et al. 2022) which will be further discussed in coming paragraphs.

There is a range of apocrine metaplastic changes, from benign to malignant. Apocrine metaplasia in a cystic lesion is frequently found in females of reproductive age and is a benign alteration. There is no connection between this metaplastic change and later growth of cancer. Papillary apocrine alteration, can be categorized as simple, complicated, and extremely complex (Quinn et al. 2022; Page et al. 1996; Choe et al. 2022). The use of CK5/6 and estrogen receptor is useful in only a few settings to distinguish between apocrine metaplasia (ER and CK5/6 negative) and ADH (ER positive, CK 5/6 negative). Other lesions commonly harboring apocrine metaplasia are fibroadenomas and hamartomas (Dupont et al. 1994). Apocrine metaplasia can be one way to distinguish phyllodes tumor from fibroadenoma in a challenged situation because it is often observed in hamartomas and fibroadenoma but not in phyllodes tumors (Quinn et al. 2022).

Atypical apocrine lesions

Apocrine ductal carcinoma in situ (DCIS)

Atypical apocrine lesions are considered as having cytological atypia (threefold fluctuation in nuclear size, hyperchromasia, and large nucleoli) (Quinn et al. 2022). Atypical apocrine adenosis is an infrequent term with unclear relevance due to comparative infrequency of presentation and paucity of clinical information. Intact lobular architecture is the key to diagnosis in any condition under consideration. Use of IHC for myoepithelial cells assists in precise judgment among many scenarios(Quinn et al. 2022).

Ductal carcinoma in situ (DCIS) exhibiting apocrine change is designated as ADCIS. The diagnosis depends on high grade features. These atypical ductal cells exhibit abundant eosinophilic and granular cytoplasm, rounded nuclei with prominent nucleoli. Other signs such as luminal necrosis, calcification and periductal alterations can also be present. The lesion is labelled as DCIS when it occupies an area of more than 2 mm in extent (Quinn et al. 2022; Bane 2013) However, this is not applicable to ADCIS.

ADCIS is recognised as a special variant. Being a rare entity, differentiation from atypical apocrine lesions and assigning accurate grade are main challenges. Nuclear grading is difficult because classic apocrine cells already have an enlarged nuclei with prominent nucleoli as compared to normal breast epithelium. That is why ADCIS should be resereved for the lesions with particular morphology that is: apocrine cells ≥ 5 times the size of benign apocrine cells. Presence of necrosis is additional identification and supportive factor. When these criteria are satisfied, a minimum size criterion (as in other kinds of DCIS / 2 mm) is not necessary(Bane 2013).

Further ADCIS does not display ER / PR expression, however, it is AR expressive. There has been evidence that HER2neu expression and the Ki67 proliferative index are substantially related with the higher nuclear grade of lesions (Leal et al. 2001). Diagnosing low-grade ADCIS is a diagnostic challenge where IHC is also of limited value. These lesions are a dilemma with variable amount of inter-observer differences. However, in such difficult circumstances, Her2neu staining may be helpful, where weak staining may point towards metaplasia/hyperplasia and strong membranous staining indicates malignant process. Similarly Ki67 and p53 expression is also helpful in such circumstances (Quinn et al. 2022).

Pleomorphic lobular carcinoma in situ with apocrine features (PALCIS)

World health organization (WHO) recognizes three LCIS subtypes: Classic, Florid and Pleomorphic. Pleomorphic LCIS (PLCIS) exhibits moderate to profound nuclear pleomorphism, intracytoplasmic vacuoles, extensive eosinophilic cytoplasm, and solid intraductal proliferation of discohesive cells, with or without apocrine features (Tan et al. 2020a, b; Zhong et al. 2020). It expresses GCDFP-15, lacks ER /PR and E-cadherin, and a small percentage can have HER-2 amplification (Quinn et al. 2022; Zhong et al. 2020).

Breast acini exhibiting pleomorphic lobular cells are frequently significantly expanded but may be only mildly distended or may show no distension at all. Even then it qualifies for pleomorphic LCIS, since there is no recognized category of pleomorphic ALH(Schnitt et al. 2020).

Core needle biopsy: a diagnostic challenge

Core needle biopsies are preferred because they are cost-effective, offer a lot of information, can be used for prognostic receptor studies and are easy to repeat. However, it also puts a diagnostic challenge as the pathologists is looking at small portion of tissue. Decoding apocrine lesions is a time taking task due to sample size limitations. Paying close attention to architectural configuration and nuclear details is important. Significant change in nuclear size (threefold increase than normal) and necrosis are worrisome features. Judicial use of IHC, discussion in multidisciplinary team meetings and radiological input is always helpful.

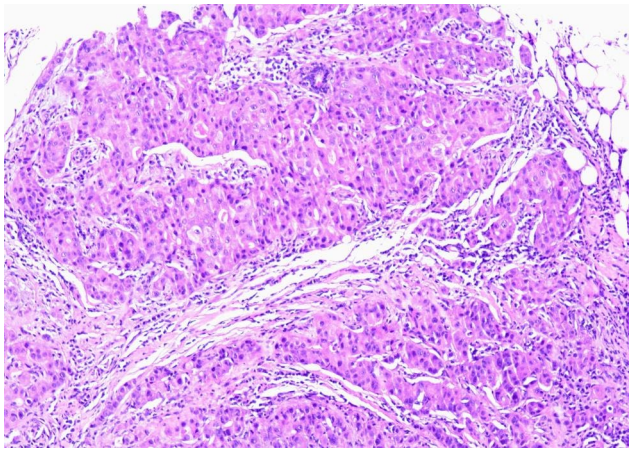

Fig. 1 H&E section, 10x showing Carcinoma with prominent apocrine differentiation

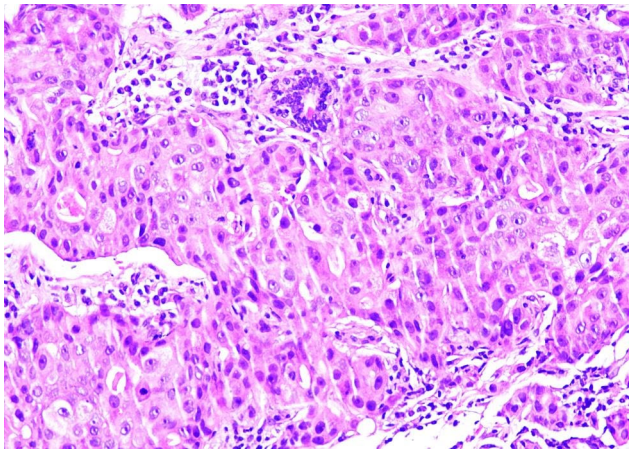

Fig. 2 H&E section, 20x exhibiting conspicuous apocrine change and nuclear pleomorphism

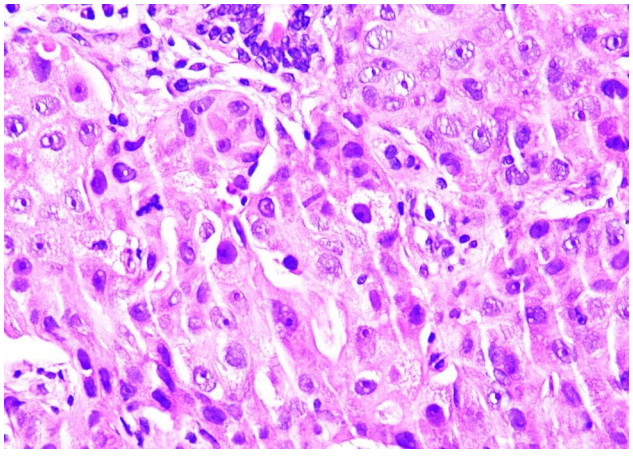

Fig. 3 H&E section, 40x, Carcinoma with apocrine differentiation morphologically having eosinophilic granular cytoplasm, distinct outlines, hyperchromatic nuclei and prominent nucleoli

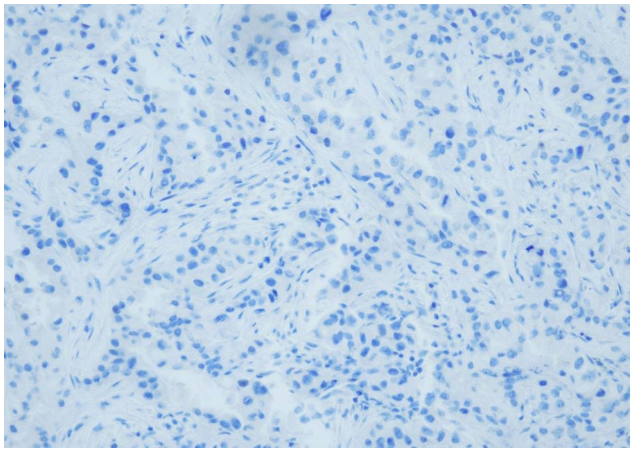

Fig. 4 Tumor cells are negative for Estrogen receptor (IHC).

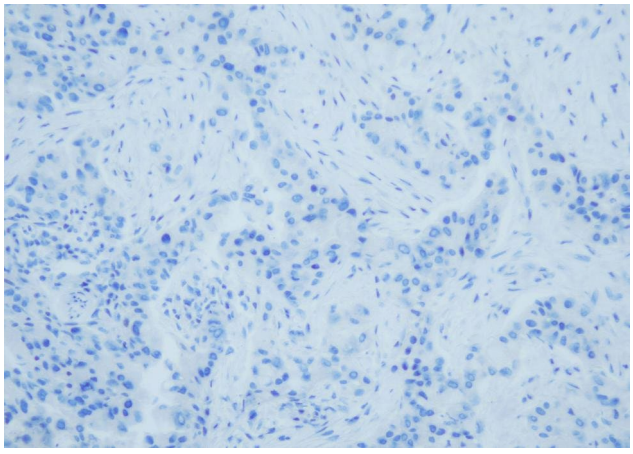

Fig. 5 Tumor cells are negative for Progesteron receptor (IHC).

Apocrine carcinoma of breast

Although there are several ways to classify breast cancers, the (WHO) focuses its categories on histological morphology (Tan et al. 2020a, b; Eble et al. 2003; Lakhani et al. 2012; Louis et al. 2021). Term Apocrine carcinoma was first coined by Krompecher in 1916, later branded by Frable and Kay in 1968 (Saridakis et al. 2021).

Apocrine carcinoma has remained an exceptional subtype, making up upto 1–4% of all cases (Vranic and Gatalica 2022; Liao et al. 2018; Hu et al. 2022; Nascimento and Otoni 2020; Yılmaz et al. 2018). The term "Invasive carcinoma with apocrine differentiation" is suggested in the 2019 version of the WHO blue book(Tan et al. 2020a, b), despite the fact that other terms have previously been used. Histologically, these tumors have large cells, an abundance of eosinophilic granular cytoplasm, enlarged nuclei, and conspicuous nucleoli in major portion of tumor (Figs. 1, 2, and 3). WHO's essential and desirable criteria defines it as a tumor having apocrine morphology in more than 90% of tumor, ER /PR negative (Figs. 4 and 5) and AR positive receptor profile (Fig. 6) (Tan et al.

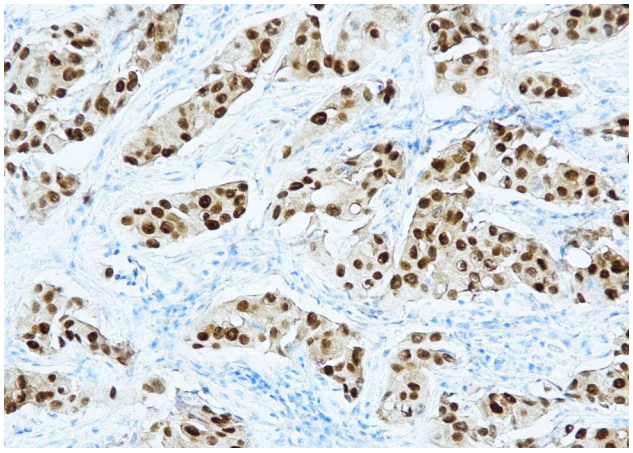

Fig. 6 Strong nuclear expression for androgen receptor in tumor cells (IHC)

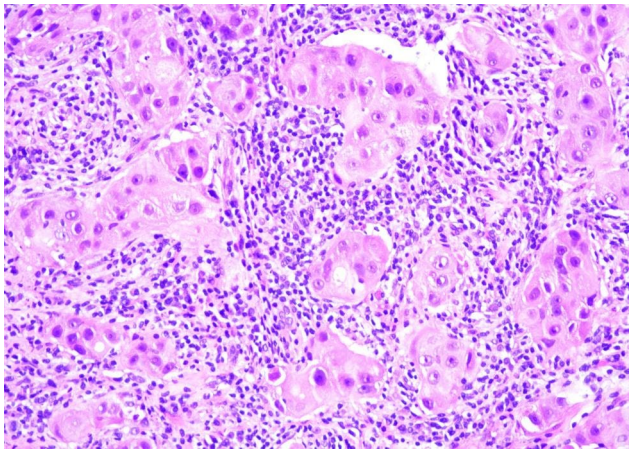

Fig. 7 Lymph node with metastatic disease from breast carcinoma with apocrine differentiation

2020a, b; Nascimento and Otoni 2020; Cserni 2020; Eble et al. 2003; Lakhani et al. 2012; Louis et al. 2021; Saridakis et al. 2021). These tumors have AR pathway activation on molecular level without ER activation (Tan et al. 2020a, b; Hu et al. 2022; Nascimento and Otoni 2020).

These tumors have higher histological grade (Saridakis et al. 2021; Nascimento and Otoni 2020; Yılmaz et al. 2018), are sporadic and typically affect elderly women. Usually presenting with clinically palpable mass with poorly defined margins on radiology screening (Vranic and Gatalica 2022; Eble et al. 2003; Lakhani et al. 2012; Louis et al. 2021; Saridakis et al. 2021; Nascimento and Otoni 2020; Yılmaz et al. 2018; Cserni 2020). LVI and LNM (Fig. 7) is much more common (Yılmaz et al. 2018; Lerner et al. 2023).

Other invasive carcinoma subtypes may also exhibit apocrine morphology such as Invasive micropapillary carcinoma, Mucinous carcinoma and Pleomorphic lobular carcinoma (Quinn et al. 2022). The differential

Table 1 Differential diagnosis of Invasive carcinoma with apocrine differentiation

Tumor type	Histology	IHC
Invasive breast carcinoma of no special type	No apocrine morphology / Apocrine morphology less than 90%	ER +/-, AR +/-
Carcinoma with apocrine differentiation	Apocrine morphology in more than 90% of tumor	ER / PR -, AR +, Her2neu +/-
Granular cell tumor:	Large, round to polygonal tumor cells with pink granular cytoplasm and central small nuclei	Positive for S100 and CD68; negative for CKs
Apocrine DCIS	DCIS with apocrine cytology, Myoepithelial cells intact	ER -, AR +
Apocrine adenosis / atypical apocrine adenosis	Preserved lobular architecture, proliferation with apocrine morphology, stromal fibrosis / sclerosis, Myoepithelial layer intact	Not needed
Histiocytic proliferations	Pale to foamy cytoplasm without nuclear atypia	CD68 +

diagnosis includes atypical apocrine adenosis, granular cell tumor, and carcinoma with oncocytic pattern, Table 1 (Vranic and Gatalica 2022; Quinn et al. 2022). Here it is important to mention that other breast cancers can also have AR expression, however, for labelling a cancer for apocrine differentiation, one needs to have all essential criteria fulfilled as set by WHO.

On IHC level, Carcinoma with apocrine differentiation are associated with positive expression of AR and variable expression of GCDFP-15 and GATA-3 (Quinn et al. 2022; Hu et al. 2022; Nascimento and Otoni 2020; Cserni 2020). As discussed above, this distinct entity is described as having ER / PR receptors negative status (Saridakis et al. 2021; Hu et al. 2022) and AR expression (in at least 10% of tumor cells) (Vranic and Gatalica 2022; Quinn et al. 2022; Saridakis et al. 2021; Hu et al. 2022; Cserni 2020). It should be kept in mind that AR is not a specific marker for apocrine carcinoma, instead it is distinctive feature of this subtype (Vranic and Gatalica 2022). On applying a strict criteria, carcinomas with apocrine differentiation can either be triple negative or HER2neu enriched (Fig. 8) (Saridakis et al. 2021; Hu et al. 2022; Vranic et al. 2015). These carcinoma also have P53 and epidermal growth factor receptor (EGFR) over expression (Liao et al. 2018).

Her2neu expression is studied in research done by Skenderi et al. (2022) in which apocrine carcinoma of the breast was observed to expresses HER2neu in 30–50% of cases. The study also explored the clinicopathological features and outcomes of HER2 positive apocrine carcinoma as compared to HER2 positive no special type carcinoma cohort. In a group of 259 cases it was observed

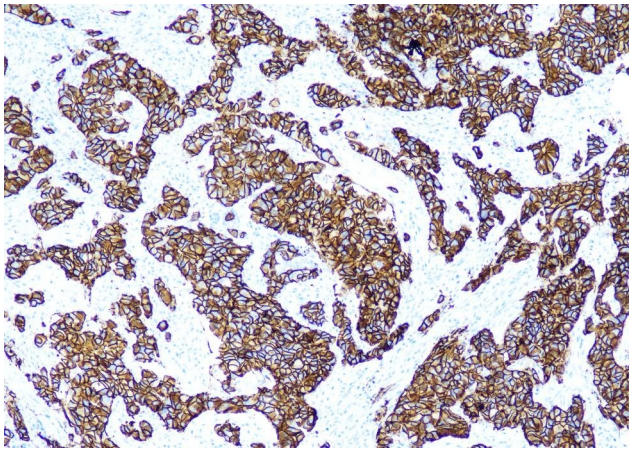

Fig. 8 Strong, complete membranous staining for HER2neu (IHC).

Table 2 Summary of the relevant morphologic, immunohistochemical, cytogenetic, molecular and clinical characteristics of apocrine carcinoma of the breast

Morphology	**Cells with distinctive margins, pink granular cytoplasm, prominent nucleoli**
Apocrine markers	GCDFP-15 positive, AR positive
Receptor profile	ER negative, AR positive, Her-2neu positive in 1/3 cases
Cytogenetic characteristics	Gains of 1q, 2q, 1p, 7, and 17 gains, 1p, 22q, 17q, 12q, and 16q loss. TP53 and PIK3CA / PTEN / AKT genes

GCDFP-15 (Gross cystic disease fluid protein 15), AR (Androgen receptor), ER (Estrogen receptor), Her2neu (human epidermal growth factor receptor 2, also called ERBB2).

that the apocrine carcinoma with Her2neu expression was common in older age with lower histological grade, tends to have a less aggressive phenotype and a more favorable outcome(Skenderi et al. 2022).

α-Methylacyl CoA racemase (AMACR) is a protein that has been found to be overexpressed in apocrine carcinoma of the breast(Nakamura et al. 2021). That is why, AMACR expression can be another prospective diagnostic pointer in apocrine lesions of breast. Its association with apocrine lesions have been previously investigated and was observed in various studies (Lerner et al. 2023; Vranic et al. 2015; Nakamura et al. 2021). In contrast to benign breast lesions, ADCIS and carcinoma with apocrine differentiation showed higher AMACR expression. It has various applications as follows:

- Diagnostic marker: AMACR was expressed in 97.4% of carcinomas with apocrine differentiation and in 96.4% of ductal carcinomas in situ with apocrine morphology with nearly uniform expression (Nakamura et al. 2021; Gatalica et al. 2022).
- Prognostic marker: High AMACR expression predicted worse prognosis among both triple negative and Her2 expressive apocrine breast cancer cohorts(Lerner et al. 2023). AMACR was overexpressed in 42 of 160 invasive carcinomas, associated with a decrease in tumor differentiation, a feature of aggressiveness (Gatalica et al. 2022).

Nevertheless, further research is required to deeply study the biochemical and clinical importance of this protein in apocrine carcinomas.

AR expression in at least 1% of tumor was considered acceptable in a research by Yue et al. in which AR immunoreactivity was studied in depth. AR expression in triple negative breast cancers (TNBC) were mostly seen in older women, larger tumors, apocrine subtypes and higher histological grades. These tumors also had frequent lymphovascular invasion. It was observed that this subset also exhibited EGFR, CK5/6 and demonstrated a negative correlation with Ki67 proliferation index which was statistically noteworthy. Given this, it should come to us as no surprise that this group exhibited a poor pathological response to chemotherapy, because we are aware that chemotherapeutic agents are most active against tumors with a high proliferative activity (Astvatsaturyan et al. 2018).

Genetic profile of carcinoma with apocrine differentiation

Carcinoma with apocrine differentiation has shown to have a distinctive molecular landscape (Sun et al. 2020), further pointed out in Table 2. Sun et al. (2020). Worth mentioning is the fact, that patients who harbor germline PTEN mutation can acquire apocrine subtype of breast cancer.

Luminal androgen receptor tumors

Based on analysis of gene expression information, another peculiar molecular apocrine subtype has been determined, which is defined by constant AR upheaval and a lack of ER expression (with or without HER2neu activity) (Vranic and Gatalica 2022). Additionally, these tumors mostly have luminal characteristics (expression of luminal CKs, lack of basal features) and are therefore called Luminal androgen receptor (LAR) tumors (Nascimento and Otoni 2020), which is one of the four molecular subtypes of TNBC (Hu et al. 2022). These molecularly defined types have a modest proliferative rate and makes up between 15 and 20% of all TNBC (Hu et al. 2022). Distant metastases are often reported to develop after three years' time (Masuda et al. 2013).

It is crucial to mention that histologically and IHC defined apocrine carcinomas (ER / PR Negative /AR positive) do not always correspond with molecularly defined apocrine carcinomas. Having said this, it is also essential to remind, that there is an estimated 70–80% overlap between the two tumor categories. About 1/3 of

histologically identified apocrine carcinomas have HER-2neu overexpression whereas most LAR carcinomas exhibit a triple-negative phenotype (Bonnefoi et al. 2016). It is emphasized that these tumors are not entirely equivalent (Vranic and Gatalica 2022; Quinn et al. 2022).

Bonnefoi et al. (2016), established with the help of IHC and genomics that there was 88% agreement between the two types. They also found lowest pathological response was observed in LARs among four molecular types (Hu et al. 2022).

Clinical implications

Apocrine carcinomas are still frequently recognized by their morphologic characteristics. Conflicting and varying published literature is attributed to the absence of clearly established diagnostic criteria. It is advised that pathologists should utilize an innovative diagnostic methodology, combining distinctive tumor morphology along with a steroid receptor profile in the light of current WHO classification of breast tumors. This will increase apocrine cancer reporting uniformity and diagnostic accuracy, which eventually will assist in identifying this unusual tumor type. The said approach, in our humble view, will substantially improve the detection of apocrine cancer which will further help us in accurate research. As our knowledge of tumor biology increases and novel therapies become accessible, it is anticipated that clinical practice will place more emphasis on the identification of morphologically pure apocrine carcinomas and molecularly defined LAR in future.

Clinical behavior and response to treatment

Due to the use of different classifications, information on the behavior of apocrine cancer is unreliable and complicated to construe. When apocrine carcinoma with triple negative profile (ACTN) were compared to other TNBC, ACTNs were seen to have better overall disease-free survival rates (Hu et al. 2022). AR expression was observed to have a favorable prognosis (Liao et al. 2018; Niemeier et al. 2010; Bozovic-Spasojevic et al. 2017; Meattini et al. 2018; Akashi et al. 2020) in another study with sample size of 41 patients (followed for 32.8 months) by Hu et al. (2022, 2018) This brings us to think that there might be potential value of anti-androgen receptor medication and chemotherapy de-escalation in ACTNs. Deep research and understanding between different molecular subtypes can help us comprehend these intricate interactions (Saridakis et al. 2021). Another prominent study performed on LARs and basal like tumors (TNBC) was done by Lehmann et al. which showed that LARs had decreased overall survival (Lehmann-Che et al. 2013).

In another detailed and comprehensive scientific research, comparable prognosis was seen between ACTNs with and without chemotherapy, which indicates space for de-escalation in the management of ACTN. Nagao et al. reported that none of his patients with invasive apocrine cancer benefitted from neoadjuvant chemotherapy. There's been insufficient clinical proof of neoadjuvant chemotherapy's effectiveness in ACTN patients. Despite apparent and visible differences in morphology and molecular profiles, the ACTN and TNBC are still treated in the same manner. Mounting data indicates that standard chemotherapy is of little therapeutic value in ACTN patients (Hu et al. 2022).

Beside Her2 targeted treatment in Her2neu amplified apocrine carcinomas, ACTN disease has limited treatment options. AR-expressing cell lines are sensitive to AR inhibitors, such as bicalutamide and enzalutamide. Nonetheless, the response of ACTN to anti-AR therapy is still fundamentally unfamiliar due to the inadequate reported ACTN cases (Quinn et al. 2022; Hu et al. 2022). However, Early clinical investigations of anti-androgen treatment have shown promising results in individuals with AR-positive, ER-negative breast disease (Bonnefoi et al. 2016; Gucalp and Traina 2017). As carcinomas with apocrine differentiation frequently harbors TP53 and PIK3CA/PTEN/AKT genes mutation, it most likely offers potential for cyclin-dependent kinases 4 and 6 (CDK4/6) inhibitor therapy (Quinn et al. 2022). Yet other studies showed low to modest therapeutic benefits of antiandrogens in a mixed group of AR positive breast carcinomas (Bonnefoi et al. 2016).

Conclusion

The diagnostic accuracy will be enhanced as a result of current discoveries and research. This takes us to the point where we are in agreement that apocrine carcinoma of breast should follow a strict and structured diagnostic approach. The algorithm should follow morphological appearance, Hormone receptor profile and Androgen expression. Where needed molecular origin of the tumor should be investigated. Such initiatives could help lessen the wide variation and inconsistency in the clinical, molecular, and definitional aspects of apocrine carcinomas.

Appropriately identified apocrine carcinoma will help us develop a cohort of cases which could lead us to consistent results in research and deep understanding of its behavior. Conflicting results among various studies regarding tumor biology, behavior, chemotherapeutic response and long term prognosis can be lessened when a basket is constructed with pure apocrine carcinomas.

Beside Her-2neu targeted treatment, advanced apocrine disease has limited treatment options. The available data suggests that (neo) adjuvant chemotherapy has a modest therapeutic advantage for AR positive breast cancers, particularly those of the apocrine subtype. Possible role of chemotherapy de-escalation and introduction of

new promising agents should be investigated with large cohort of cases and following them for suitable time. Since there is currently little information available, more research is required to better comprehend the advantage of antiandrogens agents in AR-dependent breast carcinomas. Broad genomic apocrine tumor profiling seems to be an encouraging strategy that may help identify prospective therapeutic targets.

Acknowledgements
We acknowledge Pathology Department – Aga Khan University Hospital for their technical support.

Authors' contributions
SA – Idea, concept, literature search, manuscript writing, proofreading, editing. MM - Idea, concept, proofreading. AR Proofreading and technical help. YS Proofreading. LV Proofreading.

Funding
This review article is non funded.

Data Availability
Not applicable.

Declarations

Competing interests
The authors declare that they have no competing interests.

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Received: 5 May 2023 / Accepted: 9 October 2023
Published online: 10 November 2023

References

Abbasi F, Abbasi A, Hazrati Z. Histopathologic changes of non-tumoral breast tissue in patients with invasive carcinoma of breast. Int J Res App Basic Med Sci. 2019;5(2):116–20.

Akashi M, Yamaguchi R, Kusano H, Ogasawara S, Abe E, Obara H, et al. Androgen receptor expression is useful to predict the therapeutic effect in HER2-positive breast carcinoma. Breast Cancer Res Treat. 2020;184:277–85.

Alencar NNd, Souza DAd, Lourenço AA, Silva RR. Sebaceous breast carcinoma. Autopsy and Case Reports. 2022;12.

Astvatsaturyan K, Yue Y, Walts AE, Bose S. Androgen receptor positive triple negative Breast cancer: clinicopathologic, prognostic, and predictive features. PLoS ONE. 2018;13(6):e0197827.

Bane A. Ductal carcinoma in situ: what the pathologist needs to know and why. International Journal of Breast Cancer. 2013;2013.

Bonnefoi H, Grellety T, Tredan O, Saghatchian M, Dalenc F, Mailliez A, et al. A phase II trial of abiraterone acetate plus prednisone in patients with triple-negative androgen receptor positive locally advanced or metastatic Breast cancer (UCBG 12 – 1). Ann Oncol. 2016;27(5):812–8.

Bozovic-Spasojevic I, Zardavas D, Brohée S, Ameye L, Fumagalli D, Ades F, et al. The prognostic role of androgen receptor in patients with early-stage Breast Cancer: a Meta-analysis of clinical and gene expression DataAndrogen receptor in early Breast Cancer: Meta-analysis. Clin Cancer Res. 2017;23(11):2702–12.

Choe AI, Kasales C, Mack J, Al-Nuaimi M, Karamchandani DM. Fibrocystic changes of the breast: radiologic–pathologic correlation of MRI. J Breast Imaging. 2022;4(1):48–55.

Cserni G. Histological type and typing of breast carcinomas and the WHO classification changes over time. Pathologica. 2020;112(1):25.

do Nascimento RG, Otoni KM. Histological and molecular classification of Breast cancer: what do we know. Mastology. 2020;30:e20200024.

Dupont WD, Page DL, Parl FF, Vnencak-Jones CL, Plummer WD Jr, Rados MS, et al. Long-term risk of Breast cancer in women with fibroadenoma. N Engl J Med. 1994;331(1):10–5.

Eble JN, Tavassoli FA, Devilee P. Pathology and genetics of tumours of the breast and female genital organs. Iarc; 2003.

Gatalica Z, Stafford P, Vranic S. Alpha-methylacyl-CoA racemase (AMACR) protein is upregulated in early proliferative lesions of the breast irrespective of apocrine differentiation. Hum Pathol. 2022;129:40–6.

Giaquinto AN, Broaddus RR, Jemal A, Siegel RL. The changing landscape of gynecologic cancer mortality in the United States. Obstet Gynecol. 2022;139(3):440–2.

Gucalp A, Traina TA. Androgen receptor-positive, triple-negative Breast cancer. Cancer. 2017;123(10):1686–8.

Hu T, Liu Y, Wu J, Hu XL, Zhao G, Liang B, et al. Triple-negative apocrine breast carcinoma has better prognosis despite poor response to neoadjuvant chemotherapy. J Clin Med. 2022;11(6):1607.

Lakhani SR, Ellis IO, Schnitt S, Tan PH, van de Vijver M. WHO Classification of Tumours of the Breast. 2012.

Leal C, Henrique R, Monteiro P, Lopes C, Bento MJ, de Sousa CP, et al. Apocrine ductal carcinoma in situ of the breast: histologic classification and expression of biologic markers. Hum Pathol. 2001;32(5):487–93.

Lehmann-Che J, Hamy A-S, Porcher R, Barritault M, Bouhidel F, Habuellelah H, et al. Molecular apocrine breast cancers are aggressive estrogen receptor negative tumors overexpressing either HER2 or GCDFP15. Breast Cancer Res. 2013;15:1–11.

Lerner G, Tang H, Singh K, Golestani R, St Claire S, Humphrey PA, et al. AMACR expression is a potential diagnostic marker in apocrine lesions of breast, and is Associated with high histologic Grade and Lymph Node metastases in some invasive apocrine breast cancers. Clin Breast Cancer. 2023;23(2):199–210.

Liao H-Y, Zhang W-W, Sun J-Y, Li F-Y, He Z-Y, Wu S-G. The clinicopathological features and survival outcomes of different histological subtypes in triple-negative Breast cancer. J Cancer. 2018;9(2):296.

Louis DN, Perry A, Wesseling P, Brat DJ, Cree IA, Figarella-Branger D, et al. The 2021 WHO classification of tumors of the central nervous system: a summary. Neurooncology. 2021;23(8):1231–51.

Masuda H, Baggerly KA, Wang Y, Zhang Y, Gonzalez-Angulo AM, Meric-Bernstam F, et al. Differential Response to Neoadjuvant Chemotherapy among 7 Triple-negative Breast Cancer Molecular SubtypesDifferential Response to Chemotherapy by TNBC Subtype. Clin Cancer Res. 2013;19(19):5533–40.

Meattini I, Pezzulla D, Saieva C, Bernini M, Orzalesi L, Sanchez LJ, 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–e80.

Nakamura H, Kukita Y, Kunimasa K, Kittaka N, Kusama H, Nakayama T, et al. α-Methylacyl-CoA racemase: a useful immunohistochemical marker of breast carcinoma with apocrine differentiation. Hum Pathol. 2021;116:39–48.

Niemeier LA, Dabbs DJ, Beriwal S, Striebel JM, Bhargava R. Androgen receptor in Breast cancer: expression in estrogen receptor-positive tumors and in estrogen receptor-negative tumors with apocrine differentiation. Mod Pathol. 2010;23(2):205–12.

Page DL, Dupont WD, Jensen RA. Papillary apocrine change of the breast: associations with atypical hyperplasia and risk of Breast cancer. Cancer epidemiology, biomarkers & prevention: a publication of the American Association for Cancer Research. Cosponsored by the American Society of Preventive Oncology. 1996;5(1):29–32.

Quinn CM, D'Arcy C, Wells C. Apocrine lesions of the breast. Virchows Arch. 2022:1–13.

Saridakis A, Berger ER, Harigopal M, Park T, Horowitz N, Le Blanc J, et al. Apocrine Breast cancer: unique features of a predominantly triple-negative Breast cancer. Ann Surg Oncol. 2021;28(10):5610–6.

Schnitt SJ, Brogi E, Chen Y-Y, King TA, Lakhani SR. American registry of pathology expert opinions: the spectrum of lobular carcinoma in situ: diagnostic features and clinical implications. Annals of Diagnostic Pathology. 2020;45:151481.

Skenderi F, Alahmad MAM, Tahirovic E, Alahmad YM, Gatalica Z, Vranic S. HER2-positive apocrine carcinoma of the breast: a population-based analysis of treatment and outcome. Breast Cancer Res Treat. 2022;193(2):523–33.

Sun X, Zuo K, Yao Q, Zhou S, Shui R, Xu X, et al. Invasive apocrine carcinoma of the breast: clinicopathologic features and comprehensive genomic

profiling of 18 pure triple-negative apocrine carcinomas. Mod Pathol. 2020;33(12):2473–82.
Tan PH, Ellis I, Allison K, Brogi E, Fox SB, Lakhani S et al. The 2019 World Health Organization classification of tumours of the breast. 2020a.
Tan PH, Ellis I, Allison K, Brogi E, Fox SB, Lakhani S et al. The 2019 WHO classification of tumours of the breast. Histopathology. 2020b.
Vranic S, Gatalica Z. An update on the molecular and clinical characteristics of apocrine carcinoma of the breast. Clin Breast Cancer. 2022;22(4):e576–e85.
Vranic S, Marchiò C, Castellano I, Botta C, Scalzo MS, Bender RP, et al. Immunohistochemical and molecular profiling of histologically defined apocrine carcinomas of the breast. Hum Pathol. 2015;46(9):1350–9.
Yılmaz TU, Trabzonlu L, Güler SA, Baran MA, Pösteki G, Erçin C, et al. Characteristics of special type breast tumors in our center. Eur J Breast Health. 2018;14(1):17.
Zhong E, Solomon JP, Cheng E, Baum J, Song W, Hoda SA. Apocrine variant of pleomorphic lobular carcinoma in situ: further clinical, histopathologic, immunohistochemical, and molecular characterization of an emerging entity. Am J Surg Pathol. 2020;44(8):1092–103.

Publisher's Note