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Review

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Cutaneous and Breast Apocrine Carcinoma: A Diagnostic Dilemma Between Two Mimicking Malignancies Particularly in Axillary Tumors

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Abstract

Cutaneous apocrine carcinoma is an extremely rare adnexal malignancy arising from cutaneous apocrine sweat glands, with an incidence of approximately 0.14–0.18 cases per million person-years. In contrast, breast apocrine carcinoma is an uncommon subtype accounting for approximately 0.4–4% of all breast cancers and represents a carcinoma of mammary epithelial origin showing apocrine metaplasia rather than a tumor arising from apocrine sweat glands. Despite their distinct tissue origins, these tumors share strikingly similar histopathological and immunohistochemical features because of their common apocrine differentiation. Accurate distinction is clinically important because cutaneous apocrine carcinoma generally carries a poorer prognosis, whereas breast apocrine carcinoma has been reported to have a more favorable outcome than non-apocrine triple-negative breast cancer and is managed according to breast cancer treatment strategies. The diagnostic challenge becomes particularly evident when apocrine carcinoma arises in the axilla, where both tumors may occur. The axilla is not only one of the most common sites of cutaneous apocrine carcinoma because of its abundance of apocrine sweat glands, but also the most common site of ectopic breast tissue, from which breast apocrine carcinoma may arise. However, because of the rarity of both tumors, systematic comparative studies remain limited, and no reliable diagnostic strategy has yet been established. We reviewed the available clinicopathological, immunohistochemical, and molecular evidence comparing cutaneous and breast apocrine carcinoma, with particular emphasis on diagnostic challenges in the axillary region. Overall, conventional apocrine markers, including androgen receptor (AR) and gross cystic disease fluid protein 15 (GCDFP-15), consistently supported apocrine differentiation but showed substantial overlap between the two entities. Although several markers, including estrogen receptor (ER), trichorhinophalangeal syndrome type 1 (TRPS1), tumor protein p63 (p63), cytokeratin 5/6 (CK5/6), cytokeratin 14 (CK14), and podoplanin (PDPN), demonstrated differential expression tendencies, none showed sufficient consistency to serve as a stand-alone diagnostic marker because of limited cohort sizes and methodological heterogeneity across studies. These findings highlight the current limitations of immunohistochemistry alone for determining tumor origin. Emerging transcriptome-based molecular approaches may provide complementary diagnostic information and represent a promising future direction for improving the differential diagnosis of these rare tumors.

Keywords: Breast apocrine carcinoma; Cutaneous apocrine carcinoma; Differentiation; Axillary tumor

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Introduction

Apocrine carcinoma is a rare malignancy arising from apocrine sweat glands of the skin [1]. However, there is also a subtype of breast cancer known as breast apocrine carcinoma [2]. Unlike apocrine carcinoma from the skin, also known as cutaneous apocrine carcinoma, breast apocrine carcinoma does not arise from apocrine sweat glands but from mammary epi-

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thelium that undergoes apocrine metaplasia [3]. Despite their different tissue origins, cutaneous and breast apocrine carcinomas share remarkably similar histopathological and immunohistochemical features [4], which creates a clinical challenge because these tumors differ substantially in clinical behavior, therapeutic responsiveness, and prognosis [1, 4, 5].

Distinguishing these two tumors becomes particularly challenging when apocrine carcinoma occurs in the axilla. The axilla is rich in apocrine sweat glands [6] and is also the most common site of ectopic breast tissue [7], allowing both cutaneous apocrine carcinoma and ectopic breast apocrine carcinoma to arise in this region. Because these tumors differ substantially in clinical behavior, therapeutic responsiveness, and prognosis, accurate distinction is clinically important [1, 4, 5].

Although numerous case reports have highlighted this diagnostic dilemma, a comprehensive comparison of the clinicopathological and immunohistochemical features of cutaneous and breast apocrine carcinoma remains lacking. This review summarizes the current evidence regarding their clinicopathological characteristics, diagnostic challenges, and potential future diagnostic strategies.

What Is Apocrine

Apocrine sweat gland in the skin

Apocrine glands are a type of sweat gland first described by Krause in 1844 as glands located in specific regions such as the axilla and anogenital region and are larger than those distributed over the general body surface [8]. They were later termed "apocrine sweat glands" by Schiefferdecker in 1922, based on the concept that their secretion occurs through the release of the apical portion of secretory cells [8], a process known as decapitation secretion. Structurally, apocrine glands originate from the hair germ and are composed of a coiled secretory portion and a duct, which typically opens into the hair follicle [9]. The secretory portion consists of a single layer of columnar epithelial cells resting on myoepithelial cells, whereas the ductal portion is composed of a double layer of basophilic cells with a periluminal eosinophilic cuticle [10, 11]. From an evolutionary perspective, apocrine glands are considered to represent a remnant of odoriferous organs observed in many animals [12]. They produce a viscous, lipid-rich secretion containing proteins, steroids, and ammonia. In many species, apocrine glands function as scent glands involved in pheromone production and social or sexual communication [13]; however, this role is relatively rudimentary in humans. Although apocrine glands are present at birth, they do not become functionally active until puberty [12, 14], suggesting regulation by sex hormones. Accordingly, apocrine glands express receptors for these hormones, including the androgen receptors (ARs) [15].

Apocrine cells in the breast

Interestingly, apocrine cells are also frequently observed in mammary epithelium, despite the absence of native apocrine glands in the breast [16]. These cells are thought to arise through apocrine metaplasia of mammary epithelium, rather than representing true apocrine glands [17, 18], although the molecular mechanisms underlying this phenomenon remain poorly understood. Nevertheless, they closely resemble cutaneous apocrine sweat glands histologically [3], being characterized by large columnar cells with abundant eosinophilic granular cytoplasm and enlarged nuclei with prominent nucleoli [19]. Autopsy studies have reported apocrine metaplasia in approximately half of women without a history of breast cancer, although the reported prevalence varies considerably among studies [18]. Some reports have suggested a higher prevalence in younger individuals, with frequencies ranging from approximately 20% in women aged 50–104 years to 85% in those aged 30–54 years [20]. Other studies have reported a higher frequency of apocrine metaplasia in cancer-associated breasts, reaching up to 95% [21], whereas others found no substantial difference between cancer-associated and non-cancerous breasts [22, 23].

Although apocrine metaplasia may be observed even in otherwise unremarkable mammary epithelium, it is also frequently identified in benign and proliferative breast lesions, including fibrocystic changes, cysts, fibroadenomas, papillomas, adenomas, and atypical apocrine proliferations [18–20]. In a large long-term follow-up study of 10,366 benign breast biopsies, benign papillary apocrine proliferative lesions without concurrent atypia were not associated with a significantly increased risk of subsequent breast carcinoma, although highly complex papillary apocrine change showed a trend toward increased risk [24].

In contrast, atypical apocrine lesions, including atypical apocrine adenosis and atypia within sclerosing lesions, are uncommon lesions, accounting for less than 0.4% of benign breast diagnoses [25], whose clinical significance remains uncertain. Published studies have reported conflicting findings regarding the subsequent risk of breast cancer. Some studies found no significant increase in risk compared with normal breast tissue [25–27], whereas others suggested that these lesions may represent high-risk precursor lesions [28]. Interpretation of these findings is further complicated by limited sample sizes, heterogeneous diagnostic criteria, and substantial morphological overlap with apocrine ductal carcinoma *in situ*. Furthermore, most available studies lack direct comparison with non-apocrine proliferative lesions, making it difficult to determine whether these biological behaviors are truly unique to apocrine proliferations.

Apocrine Carcinoma

The term "apocrine carcinoma" originally referred to an adnexal skin malignancy arising from cutaneous apocrine sweat glands [29]. However, carcinomas with apocrine morphology may also occur in the breast. Unlike cutaneous apocrine carcinoma, breast apocrine carcinoma does not arise from apocrine sweat glands but represents a carcinoma of mammary epithelial origin showing apocrine metaplasia. Despite their distinct tissue origins, these tumors frequently exhibit remarkably similar histopathological features. Histologically, cutaneous apocrine carcinoma is characterized by infiltrative glan-

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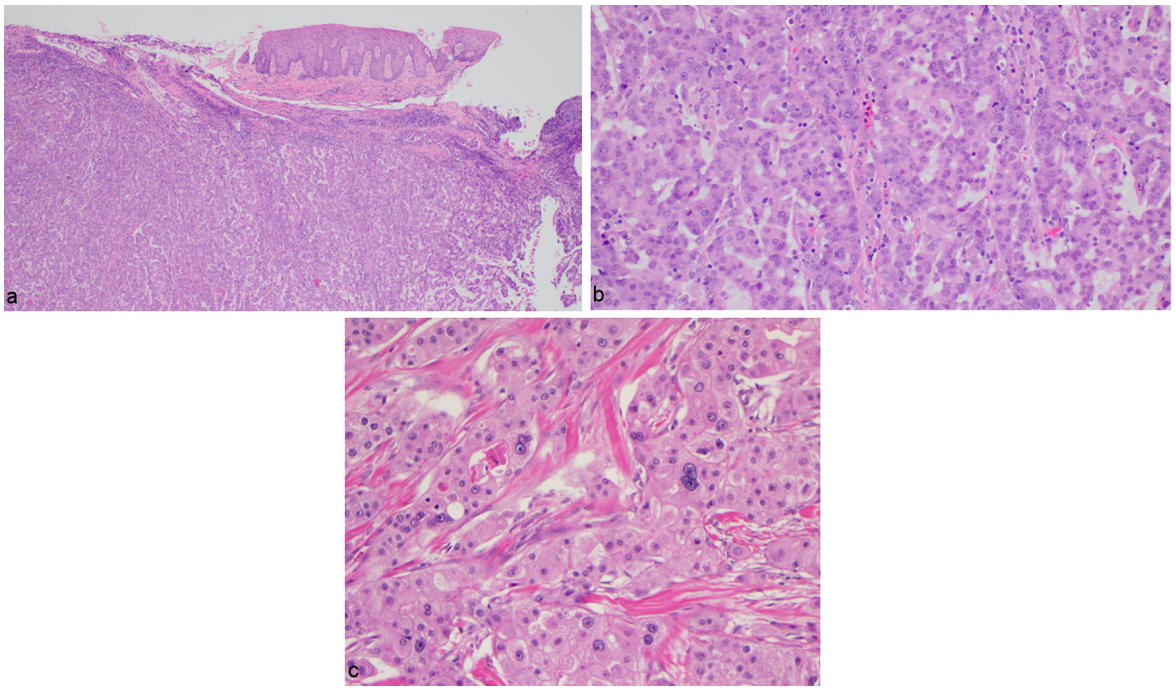


Figure 1. Representative histopathological images of cutaneous and breast apocrine carcinoma. (a) Low power field showing invasive apocrine carcinoma of the skin involving superficial dermis (H&E × 5). (b) Higher magnification showing apocrine morphology with conspicuous eosinophilic cytoplasm, enlarged nuclei and prominent eosinophilic nucleoli (H&E × 20). (c) Breast carcinoma of no special type with apocrine differentiation showing infiltrating cords of tumors cells with large polygonal tumor cells, abundant granular eosinophilic cytoplasm, and prominent eosinophilic nucleoli (H&E × 20). H&E: hematoxylin and eosin stain.

dular structures composed of large eosinophilic tumor cells with granular cytoplasm, prominent nucleoli, mitotic activity, and focal decapitation secretion (Fig. 1a, b) [1]. Breast apocrine carcinoma, currently classified as "breast carcinoma with apocrine differentiation" in the World Health Organization (WHO) classification, is defined by the presence of apocrine morphology in more than 90% of tumor cells [30]. Histologically, it is composed of large cells with abundant eosinophilic granular cytoplasm and enlarged nuclei with prominent nucleoli, closely resembling its cutaneous counterpart (Fig. 1c). Thus, both tumors represent adenocarcinomas predominantly composed of apocrine cells and share strikingly similar pathological appearances. However, despite their overlapping histopathological features, their clinical management and therapeutic approaches are distinct.

Cutaneous apocrine carcinoma

Cutaneous apocrine carcinoma typically arises in apocrine gland–rich regions, including the axilla, head and neck, and groin. It is an extremely rare malignancy; population-based analyses using the Surveillance: Epidemiology: and End Results (SEER) database have reported an incidence of approximately 0.14–0.18 cases per million person-years [31], accounting for only about 0.005% of all cutaneous carcinomas [1]. Owing to its rarity, current knowledge regarding optimal treatment strategies and prognostic factors remains limited. Historically, wide surgical excision with 1–2 cm margins has been recommended [6]. Because lymph node metastasis at initial diagnosis has been reported in 69–89% of cases, lymph node dissection has historically been performed as part of curative treatment [32–34]. However, no standardized international guideline has been established for the management of cutaneous apocrine carcinoma. More recent practice generally favors therapeutic lymph node dissection only in patients with clinically or radiologically evident nodal metastasis, although the optimal management of regional lymph nodes remains a matter of debate [1, 6]. Furthermore, no consensus has been established regarding effective systemic therapies for advanced or metastatic disease. Although several case reports have described clinical responses to regimens such as epirubicin plus cyclophosphamide followed by S-1 [35], paclitaxel plus carboplatin [36], anti-androgen therapy [37], and anti-human epidermal growth factor receptor 2 (HER2) therapy in HER2-positive tumors [38], no therapeutic regimen has yet demonstrated efficacy in large-scale studies. The prognosis has generally been reported to be relatively poor, particularly in patients with lymph node metastasis [1]. In a retrospective study of 186 patients with cutaneous apocrine carcinoma, median overall survival was reported to be approximately 55 months in patients without nodal metastasis compared with 33 months in those with nodal involvement [32].

Breast apocrine carcinoma

Breast apocrine carcinoma was first described by Krompecher in 1916 as a malignant tumor composed of apocrine-like epi-

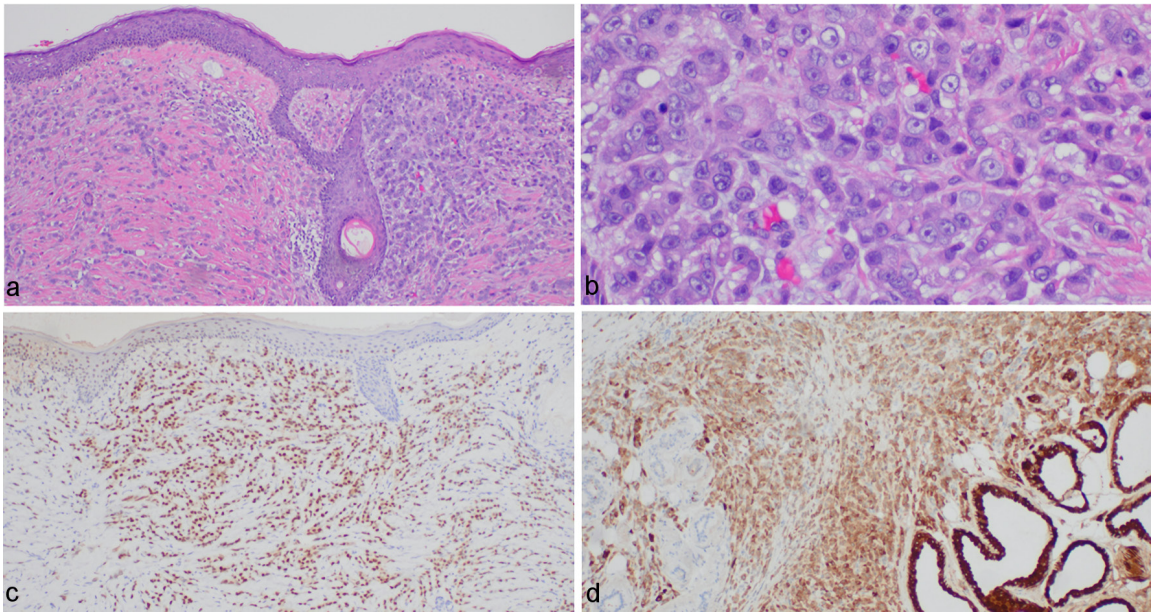


Figure 2. Representative histopathological and immunohistochemical findings of an axillary apocrine carcinoma. (a) Invasive carcinoma with apocrine differentiation involving the superficial dermis (hematoxylin and eosin stain, × 10). (b) High-power view showing large tumor cells with abundant eosinophilic granular cytoplasm, enlarged nuclei, and prominent nucleoli (hematoxylin and eosin stain, × 40). (c) Immunohistochemical staining for GCDFP-15 demonstrating diffuse tumor cell positivity. Adjacent normal apocrine glands show positive staining (right), whereas eccrine ductal cells (left) are negative (× 10). (d) Diffuse nuclear immunoreactivity for androgen receptor (AR) in tumor cells (× 10). GCDFP-15: gross cystic disease fluid protein 15.

thelial cells [39] and has been recognized as a distinct special type of breast carcinoma since the second edition of the WHO classification [2]. It accounts for approximately 0.4–4% of all breast cancers [40]. In the current WHO classification, breast apocrine carcinoma is additionally characterized by an estrogen receptor (ER)-negative and AR-positive [30]. HER2 status is variable, with approximately 30–50% of cases reported to be HER2-positive, while the remaining cases are largely classified as triple-negative breast cancer [5, 41]. Because treatment strategies generally follow those for conventional breast cancer, patients are typically managed with surgical resection combined with neoadjuvant or adjuvant chemotherapy and radiotherapy according to ER and HER2 status [5]. Notably, breast apocrine carcinoma has been reported to show a more favorable prognosis than conventional triple-negative breast cancer [42, 43]. In a SEER database analysis, the 7-year disease-specific survival was reported to be 86% in apocrine triple-negative breast cancer compared with 74% in non-apocrine triple-negative breast cancer [41, 44]. Beyond the conventional definition of pure apocrine carcinoma, the extent of apocrine morphology itself may represent a biological spectrum associated with distinct tumor characteristics. In our recent study, a greater degree of apocrine morphology was associated with lower proliferative activity and more favorable prognosis in ER-negative breast cancer, whereas the opposite associations were observed in ER-positive disease [45]. Focusing on the conventional ER-negative apocrine carcinoma phenotype, however, breast apocrine carcinoma has been reported to exhibit relatively limited responsiveness to conventional chemotherapy compared with non-apocrine triple-negative breast cancer [46–48]. More recently, immune checkpoint inhibitors have also been incorporated into the standard treatment of high-risk triple-negative breast cancer [49]. Although evidence specific to breast apocrine carcinoma remains limited, emerging data suggest potential activity of pembrolizumab-based chemoimmunotherapy in tumors with apocrine features [50, 51]. The optimal treatment strategy specifically for this subtype therefore remains a matter of debate.

Why Does Differentiation Matter?

Distinguishing between these biologically distinct yet histologically similar tumors becomes particularly important when apocrine carcinoma arises in the axilla. Figure 2 illustrates the representative histopathological and immunohistochemical findings of an axillary apocrine carcinoma case encountered at our institution. Hematoxylin and eosin staining (Fig. 2a, b) demonstrates an adenocarcinoma composed of large eosinophilic cells with abundant granular cytoplasm and prominent nucleoli. Together with diffuse AR and gross cystic disease fluid protein 15 (GCDFP-15) positivity (Fig. 2c, d), these histopathological and immunophenotypic findings are compatible with both cutaneous and breast apocrine carcinoma, requiring consideration of both entities in the pathological differential diagnosis.

What makes this diagnostic dilemma unique to the axilla is that both cutaneous and breast apocrine carcinoma may arise in this region. Unlike eccrine sweat glands, which are distributed widely throughout the body and primarily function in ther-

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moregulation, apocrine sweat glands are localized to specific anatomical regions [14]. The axilla is particularly rich in apocrine glands, with an apocrine-to-eccrine gland ratio approaching 1:1 [52]; histological studies have identified approximately 8–43 apocrine glands per cm^2 in the axillary skin [10]. Accordingly, in a retrospective study of 186 patients with cutaneous apocrine carcinoma, the axilla was the most common primary site, accounting for 53% of cases, followed by the head and neck region at 35% [32]. Meanwhile, breast tissue may also be found outside the normal breast as ectopic breast tissue. Ectopic breast tissue, thought to represent remnants of the embryologic mammary ridge [53], can arise anywhere along the embryologic milk line extending from the axilla to the groin [54], with the axilla representing the most common site [55]. It is present in approximately 2–6% of women [56, 57], and may occur even in men, although much less frequently, with a reported male-to-female ratio of approximately 2.5:100 [58]. Although rare, ectopic breast tissue can give rise to ectopic breast carcinoma, accounting for approximately 0.3–0.6% of all breast cancers [55, 59]. Consequently, the axillary region may give rise not only to cutaneous apocrine carcinoma originating from apocrine sweat glands but also to breast apocrine carcinoma arising from ectopic breast tissue. Thus, in the axilla, a unique anatomical region in which both tumors may arise, distinction is required between two remarkably similar yet clinically distinct malignancies.

Reported Cases of Axillary Apocrine Carcinoma

In clinical practice, numerous cases requiring differentiation between cutaneous and breast apocrine carcinoma in the axillary region have been reported. The reported cases are summarized in Table 1 [60–81]. We identified 22 English-language case reports of axillary apocrine carcinoma in a PubMed search through August 2026 using keywords related to "apocrine carcinoma" and "axilla," regardless of the presumed origin [60–81]. Reports that did not describe the diagnostic process were excluded. Among the 23 patients, the median age was 61 (33–92) years, with 19 male (83%) and four female (17%) patients. The median tumor size was 40 (4–120) mm.

Interestingly, in 21 (91%) of the 23 cases, both cutaneous and breast apocrine carcinoma were considered during the diagnostic process before one origin was ultimately favored. As the basis for diagnosis, 14 cases relied on the presence or absence of adjacent normal structures, including ectopic mammary tissue or normal apocrine glands. Seven cases cited the absence of a detectable breast primary lesion, either alone or in combination with pathological findings, as supportive evidence for diagnosis. In this differential diagnosis, three possibilities should be considered: primary cutaneous apocrine carcinoma, carcinoma arising in ectopic breast tissue, and metastatic breast carcinoma. The presence of adjacent cutaneous apocrine structures may support a primary cutaneous origin, whereas identification of ectopic mammary tissue or an *in situ* component favors carcinoma arising in ectopic breast tissue. In contrast, detection of a primary breast lesion supports metastatic breast carcinoma. On the other hand, several reported tumors exceeded 10 cm in diameter, raising the possibility that extensive tumor involvement may obscure or replace the surrounding normal structures. Therefore, absence of adjacent mammary tissue or apocrine glands should be interpreted cautiously when excluding a particular origin. Likewise, although absence of a detectable breast primary lesion may be useful in excluding metastatic breast carcinoma involving the skin or lymph nodes, this finding alone may not reliably distinguish cutaneous apocrine carcinoma from carcinoma arising in ectopic breast tissue. Although immunohistochemical findings such as GCDFP-15, cytokeratin 7 (CK7), and cytokeratin 20 (CK20) were reported in nearly all cases, only six reports explicitly described immunohistochemical findings as part of the basis for diagnosis.

Immunohistochemical Overlap Between Cutaneous and Breast Apocrine Carcinoma and Practical Diagnostic Approach

Because differentiation between cutaneous and breast apocrine carcinoma in the axillary region is often challenging based on histopathological findings alone, various immunohistochemical markers have been discussed in the literature as potential tools for determining tumor origin. Figure 3 summarizes previous studies involving cohorts of five or more cases of cutaneous and/or breast apocrine carcinoma that reported the positivity rates of immunohistochemical markers [4, 5, 82–103]. In this summary, markers with a reported positivity rate of ≥ 50% were visually categorized as "frequently positive" (shown in pink) whereas those with < 50% positivity were categorized as "less frequently positive" (shown in light blue). Because the reported cohort sizes varied substantially, this categorization should be interpreted as a visual overview rather than a strict diagnostic threshold. Also, several markers were evaluated only in one tumor type or in small cohorts, limiting direct comparison.

Overall, previously reported immunohistochemical profiles show substantial overlap between cutaneous and breast apocrine carcinoma, particularly for commonly used apocrine markers such as GCDFP-15, GATA binding protein 3 (GATA3), AR, and mammaglobin. Many of the reported cases of axillary apocrine carcinoma in which differential diagnosis was discussed (Table 1) [60–81] also employed these markers during the diagnostic process. However, these markers may support apocrine differentiation but are insufficient to reliably determine the tissue of origin when used alone.

Apocrine markers

Several immunohistochemistry (IHC) markers are characteristically expressed in apocrine cells and apocrine tumors. Among them, AR plays a central role in apocrine biology. Because normal apocrine sweat glands differentiate during puberty under the influence of sex-related hormones such as androgens [12, 14], apocrine sweat glands characteristically express AR [15]. Accordingly, AR expression is frequently observed in cutaneous apocrine carcinoma [1]. Similarly, breast

Table 1. Reported Cases of Axillary Apocrine Carcinoma

No.	Author	Age/sex	Size (mm)	Initial Dx	Final Dx	Mention both[a]	Basis (pathological findings)	Basis (clinical findings)
1	Mishima er al, 2026 [60]	57/F	20	B/C	B	Yes	Adjacent mammary tissue identified	
2	Kameh Khosh et al, 2025 [61]	60/M	66	B	C	Yes		Clinical behavior
3	Kamata et al, 2024 [62]	61/F	10	B/C	C	Yes	No adjacent mammary tissue	
4	Khessairi et al, 2024 [63]	58/M	100	C	C	Yes		No breast primary lesion
5	Libertini et al, 2020 [64]	61/M	N/A	C	C	Yes	IHC findings	
6	Sekine et al, 2020 [65]	83/F	10	C	C	Yes	No adjacent mammary tissue	
7	Benzzi et al, 2017 [66]	61/M	100	C	C	Yes		No breast primary lesion
8	Berdugo et al, 2017 [67]	71/M	50	C	C	Yes	No adjacent mammary tissue	No breast primary lesion
9	Seong et al, 2015 [68]	51/M	40	C	C	Yes		No breast primary lesion
10	Seong et al, 2015 [68]	66/M	40	C	C	Yes	No adjacent mammary tissue	No breast primary lesion
11	Zelger et al, 2008 [81]	71/M	120	B	C	Yes	Adjacent mammary tissue identified	
12	Li et al, 2022 [70]	67/M	31	B	B	Yes	No adjacent mammary tissue	No breast primary lesion
13	Kopecky et al, 2026 [69]	57/M	N/A	B/C	C	Yes	No adjacent mammary tissue	
14	Zahid et al, 2016 [71]	56/M	50	B/C	C	Yes	Adjacent apocrine glands identified + IHC findings	
15	Vasilakaki et al, 2011 [72]	67/M	10	B/C	C	Yes	No adjacent mammary tissue	No breast primary lesion
16	Pucevich et al, 2008 [73]	92/F	40	B/C	C	Yes	Histopathological findings	
17	Ahmad et al, 2024 [75]	76/M	20	C	C	No	Histopathological findings	
18	Gatti et al, 2017 [74]	72/M	64	C	C	No	IHC findings	
19	Lin et al, 2012 [76]	65/M	55	B/C	B	Yes	No adjacent apocrine glands + IHC findings	
20	Fujiwara-Tani et al, 2018 [77]	87/M	32	B/C	B	Yes	IHC findings	
21	Talukdar et al, 2022 [78]	52/M	80	C	C	Yes	Adjacent apocrine glands identified + IHC findings	
22	Kathrotiya et al, 2015 [79]	49/M	50	B/C	C	Yes	No adjacent mammary tissue	
23	Toledo-Pastrana et al, 2014 [80]	33/M	4	B/C	C	Yes	No adjacent mammary tissue	

[a]"Mention both" indicates whether both cutaneous and breast apocrine carcinoma were included in the differential diagnosis. B: breast apocrine carcinoma; C: cutaneous apocrine carcinoma; Dx: diagnosis; F: female; M: male; IHC: immunohistochemistry; N/A: not available.

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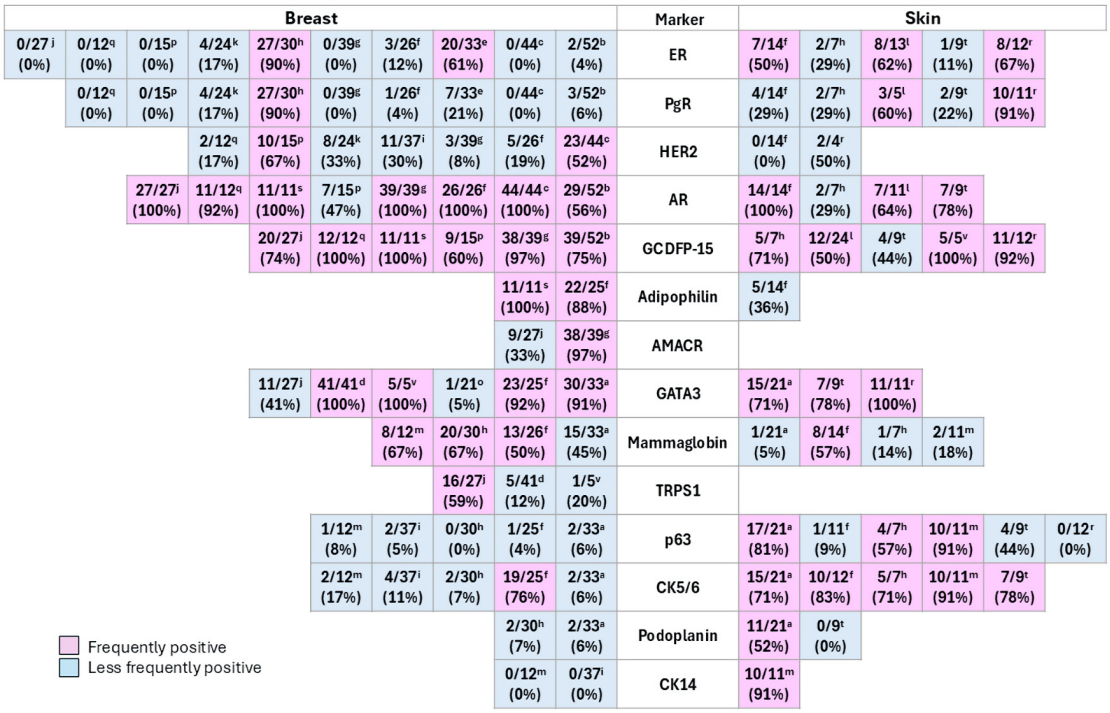


Figure 3. Summary of published immunohistochemical marker positivity in cutaneous and breast apocrine carcinoma. Each cell represents the results from a single published study. The upper line indicates the number of positive cases divided by the total number of cases, and the lower line indicates the corresponding positivity rate (%) within each study. Marker names are shown in the center column. Positivity data for breast apocrine carcinoma are displayed on the left, whereas those for cutaneous apocrine carcinoma are displayed on the right. Markers with a reported positivity rate of ≥ 50% are shown in pink (frequently positive), whereas those with a positivity rate of < 50% are shown in light blue (less frequently positive). Superscript letters in the upper right corner of each cell correspond to the reference numbers listed below. Reference key: [a][89]; [b][86]; [c][99]; [d][101]; [e][84]; [f][4]; [g][92]; [h][83]; [i][5]; [j][93]; [k][88]; [l][97]; [m][98]; [n][91]; [o][82]; [p][87]; [q][103]; [r][95]; [s][90]; [t][96]; [u][94]; [v][102]. AR: androgen receptor; GCDFP-15: gross cystic disease fluid protein 15; ER: estrogen receptor; TRPS1: trichorhinophalangeal syndrome type 1; p63: tumor protein p63; CK5/6: cytokeratin 5/6; CK14: cytokeratin 14; AMACR: alpha-methylacyl-CoA racemase; PgR: progesterone receptor; HER2: human epidermal growth factor receptor 2; GATA3, GATA binding protein 3.

apocrine carcinoma acquires AR expression through apocrine metaplasia [16], and AR positivity is currently regarded as one of its defining immunophenotypic features [30].

Several downstream targets or associated proteins of AR signaling have likewise been linked to apocrine differentiation [93]. GCDFP-15, one of the most widely used apocrine markers in clinical practice, was originally identified in gross cyst fluid of the breast and was subsequently shown to be specifically expressed in apocrine metaplastic epithelium rather than normal mammary epithelium [104, 105]. Consistent with this biology, GCDFP-15 expression has been widely reported in breast apocrine carcinoma and normal cutaneous apocrine glands, leading to its recognition as a classical marker of apocrine cells [86, 92, 104]. Accordingly, frequent positivity for GCDFP-15 has been reported in both breast and cutaneous apocrine carcinoma.

Alpha-methylacyl-CoA racemase (AMACR), a mitochondrial and peroxisomal enzyme involved in fatty acid metabolism [92], was originally established as a diagnostic marker for AR-positive prostate carcinoma [106] and has subsequently been reported in AR-positive breast carcinomas with apocrine differentiation [107]. Recent studies have further demonstrated frequent AMACR expression in a broad spectrum of mammary apocrine lesions, including apocrine metaplasia, apocrine ductal carcinoma *in situ*, and invasive apocrine carcinoma [108]. Similarly, adipophilin, a lipid droplet–associated protein also expressed in sebaceous carcinoma [109], reflects the intracytoplasmic lipid accumulation characteristic of apocrine cells. Although adipophilin positivity in cutaneous apocrine carcinoma appears relatively limited [4, 110], higher expression has been reported in tumors with apocrine differentiation, including pulmonary carcinomas with apocrine features and breast apocrine carcinoma [90, 111].

Taken together, these markers are useful for characterizing apocrine tumors and distinguishing them from non-apocrine malignancies. However, because these proteins are broadly expressed in both normal apocrine glands and tumors with apocrine differentiation, their utility for determining tissue origin appears limited.

Hormone-related markers

In breast cancer, hormone receptor status and HER2 expres-

sion play central roles in clinicopathological classification and therapeutic decision-making. Historically, breast apocrine carcinoma has been defined using various criteria, including purely morphological definitions as well as definitions combining apocrine morphology with hormone receptor status [19]. In the current WHO classification, however, carcinoma with apocrine differentiation is characterized by apocrine morphology together with an ER-negative/AR-positive immunophenotype [30]. Accordingly, most studies have reported breast apocrine carcinoma to be predominantly ER-negative and progesterone receptor (PgR)-negative. In contrast, HER2 status appears more heterogeneous, with both HER2-positive and HER2-negative cases being reported.

In cutaneous apocrine carcinoma, more than 50% positivity for ER and PgR was reported in three and two of the five available studies, respectively. In comparative studies between breast and cutaneous apocrine carcinoma, ER negativity was more frequently observed in breast apocrine carcinoma than in cutaneous apocrine carcinoma. Studies evaluating HER2 expression in cutaneous apocrine carcinoma remain limited, and reported HER2 positivity rates have varied substantially, ranging from 0% [4] to 50% [95]. Interestingly, several case reports have described favorable responses of HER2-positive cutaneous apocrine carcinoma to anti-HER2 therapy using treatment strategies adopted from breast cancer [62, 112], suggesting potential therapeutic relevance of HER2 evaluation in these tumors.

Overall, however, the significance of ER, PgR, and HER2 expression for determining tissue origin remains unclear.

Glandular and skin-associated markers

In general, breast and cutaneous carcinomas are often distinguished using lineage-associated immunohistochemical markers [113, 114]. However, this distinction is less straightforward in apocrine carcinoma because both entities share glandular morphology and apocrine differentiation [89, 98]. GATA3, mammaglobin, and trichorhinophalangeal syndrome type 1 (TRPS1) are commonly used breast lineage-associated markers [115], but their expression in apocrine carcinoma is inconsistent. GATA3 and mammaglobin show variable positivity in both breast and cutaneous apocrine carcinoma. Although TRPS1 has been proposed as a relatively breast-specific marker [116] and was historically considered negative in cutaneous apocrine glands and cutaneous apocrine carcinoma [117], more recent studies have demonstrated TRPS1 expression in these lesions [118].

In contrast, tumor protein p63 (p63) [119, 120], cytokeratin 5/6 (CK5/6) [121], cytokeratin 14 (CK14) [98], and podoplanin [122] have been described as markers associated with cutaneous adnexal differentiation. These markers were more frequently positive in cutaneous apocrine carcinoma and generally negative in breast apocrine carcinoma. Although complete separation between the two entities was not achieved, these markers may still provide supportive evidence favoring cutaneous origin. On the other hand, epidermal growth factor receptor (EGFR), which has been regarded as a basal-associated marker, is expressed in normal apocrine sweat glands and has also been reported in cutaneous apocrine carcinomas, while relatively frequent expression has additionally been observed in mammary apocrine carcinoma [100, 123, 124]. Because the available studies were small and methodologically heterogeneous, these findings should be interpreted as general expression tendencies rather than strict diagnostic criteria.

Practical diagnostic approach

In practice, differentiation between cutaneous and breast apocrine carcinoma should be based on an integrated assessment rather than on any single finding. Clinical history, tumor location and morphology, the presence or absence of adjacent apocrine glands or ectopic mammary tissue, and immunohistochemical findings should all be considered together. Conventional imaging modalities, including mammography, ultrasonography, and magnetic resonance imaging (MRI), may be useful for identifying ectopic breast tissue [125] or detecting a primary breast lesion [126]. However, clinical features such as age, sex, and disease course are not necessarily specific to either tumor type, and substantial overlap also exists in morphological and immunohistochemical findings [4]. Therefore, definitive determination of the tissue of origin may remain challenging even after comprehensive evaluation.

Conclusions and Future Directions

Cutaneous and breast apocrine carcinomas are biologically distinct malignancies arising from different organs and exhibiting markedly different clinical behaviors, prognoses, and therapeutic strategies. However, these tumors show substantial overlap in histopathological appearance and immunophenotypic features because of their shared apocrine differentiation. Although both entities are rare, numerous reports have highlighted the diagnostic difficulty encountered in distinguishing them, particularly in the axillary region. While several immunohistochemical markers showed differences in expression patterns between the two entities, currently available evidence remains limited and insufficiently reliable for routine diagnostic use.

Recent advances in transcriptomic profiling may provide new opportunities to improve the differential diagnosis of rare tumors. In our recent study, we developed a transcriptome-based molecular differentiation score to distinguish cutaneous from breast apocrine carcinoma [127]. For rare tumors such as apocrine carcinoma, the limited availability of training datasets is often a major obstacle to developing transcriptome-based diagnostic models. To address this challenge, we constructed the differentiation score using large transcriptomic cohorts representing the entire spectrum of breast and cutaneous carcinomas and subsequently validated its performance in apocrine carcinoma. These findings suggest that transcriptome-based approaches can accurately distinguish cutaneous from breast apocrine carcinoma despite the scarcity of transcriptomic data. As transcriptomic profiling becomes increasingly incorpo-

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rated into routine clinical practice, such molecular diagnostic approaches may become practical adjuncts to histopathological and immunohistochemical evaluation for distinguishing diagnostically challenging rare tumors, including apocrine carcinoma. Future large comparative studies and independent validation of molecular diagnostic tools, including transcriptome-based differentiation scores, will be important for establishing more objective and reliable diagnostic strategies for these challenging tumors.

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Conflict of Interest

The authors declare no competing financial interests.

Author Contributions

KK conceptualized and designed the study, performed statistical and bioinformatic analyses, and wrote the original draft. KT provided supervision, contributed to study design, and critically revised the manuscript. RM, EE, MO, AY, KN, TK, IE, TI critically revised the manuscript. All authors approved the final manuscript.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

Abbreviations

AMACR: alpha-methylacyl-CoA racemase; AR: androgen receptor; CK5/6: cytokeratin 5/6; CK7: cytokeratin 7; CK14: cytokeratin 14; CK20: cytokeratin 20; ER: estrogen receptor; GATA3: GATA binding protein 3; GCDFP-15: gross cystic disease fluid protein 15; HER2: human epidermal growth factor receptor 2; IHC: immunohistochemistry; PDPN: podoplanin; PgR: progesterone receptor; SEER: Surveillance, Epidemiology, and End Results; TRPS1: trichorhinophalangeal syndrome type 1; WHO: World Health Organization

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