# Diagnostic Pitfalls in Fine Needle Aspiration Cytology of Apocrine Carcinoma of the Breast: Case Report

## Memenin Apokrin Karsinomunun İnce İğne Aspirasyon Sitolojisinde Tanısal Tuzakları

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**ABSTRACT** Apocrine carcinoma of the breast is a rare type of invasive breast cancer. It is most frequently seen in the postmenopausal period as a unilateral and multicentric mass. A 76-year-old female with a left breast mass for 12 years presented with left areolar retraction and discharge, and ulceration of the breast skin. A fine needle aspiration cytology (FNAC) of the breast mass showed three dimensional clusters of atypical cells with groups in a necrotic background. Those cells were apocrine-like and had hyperchromatic nuclei, cytoplasmic vacuoles and granular cytoplasms. The cytological result was reported as "suspicious for malignancy". The patient underwent simple mastectomy. Histological examination of the excised specimen revealed apocrine carcinoma. The differential diagnosis mainly includes benign lesions, such as apocrine adenoma, atypical apocrine adenosis and granular apocrine metaplasia, in addition to apocrine carcinoma.

**Key Words:** Breast; carcinoma; diagnostic errors

**ÖZET** Memenin apokrin karsinomu, invaziv meme kanserleri arasında oldukça nadir görülür. En sık postmenapozal kadınlarda unilateral ve multisentrik olarak ortaya çıkar. Yetmiş altı yaşında kadın hasta, sol memede yaklaşık 12 yıldır şişlik ve meme başında retraksiyon, meme başı akıntısı ve meme derisinde yara oluşması şikayeti ile başvurdu. İnce iğne aspirasyon sitolojisinde (İİAS); nekroz zemininde, üç boyutlu kümeler oluşturan iri hiperkromatik nükleuslu, granüler stoplazmalı, apokrin benzeri hücreler saptanarak şüpheli malign tanısı verildi. Daha sonra yapılan basit mastektomide apokrin karsinom tanısı verildi. Apokrin hücreler varlığında preoperatif ayırıcı tanıda; apokrin adenoma, atipik apokrin metaplazi, apokrin komponentli kompleks sklerozan lezyonlar gibi benign durumların yanısıra apokrin karsinom da akılda tutulmalıdır.

**Anahtar Kelimeler:** Meme; karsinom; tanısal hatalar

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Apocrine carcinoma of the breast is a rare, unique, and morphologically distinct type of invasive breast carcinoma. It is most frequent in the sixth and seventh decades.[1] Main characteristics of apocrine carcinoma are unilaterality, multicentricity, low histological grade, lower positivity of estrogen (ER) and progesterone (PR) receptors.[2] There is uncertainty about the diagnosis and prognosis of the apocrine carcinoma of the breast due to its rarity and the absence of standard definite diagnostic criteria in the histopathological examination.[3] Apocrine changes of breast lesions can be seen in a spectrum from microscopic cysts to invasive carcinoma. Sclerosing adenosis, complex sclerosing lesions with apocrine foci,

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apocrine adenoma, atypical apocrine metaplasia and in situ and invasive carcinomas fall into this spectrum.[4,5]

Here, we aim to discuss the cytological and histopathological features of apocrine carcinoma of the breast and the differential diagnosis of other benign breast lesions within the scope of recent literature.

## CASE REPORT

A 76-year-old female with a palpable mass in her left breast for 12 years presented with left areolar retraction, purulent discharge and ulceration of the breast skin. Physical examination revealed retraction and solid mass in the left areola, and left axillary lymphadenopathy. Mammography showed a mass that involved the entire breast with centrally located cystic areas and peripheral macrocalcifications. It was hypoechoic and measured 9x12 cm. The abdominal ultrasound (US) was normal. A fine needle aspiration cytology (FNAC) was done under US guidance. Cytological examination of alcohol-fixed, Papanicolaou-stained preparations showed lots of macrophages, inflammatory cells and a few ductal epithelial cells in a necrotic background (Figure 1 a-d). Air-dried, Giemsa-stained slides showed cells that led to the strong suspicion of malignancy with three dimensional clusters of atypical cells with hyperchromatic nuclei and cytoplasmic granules and vacuoles (Figure 2). The diagnosis was reported as “strongly suspicious ma-

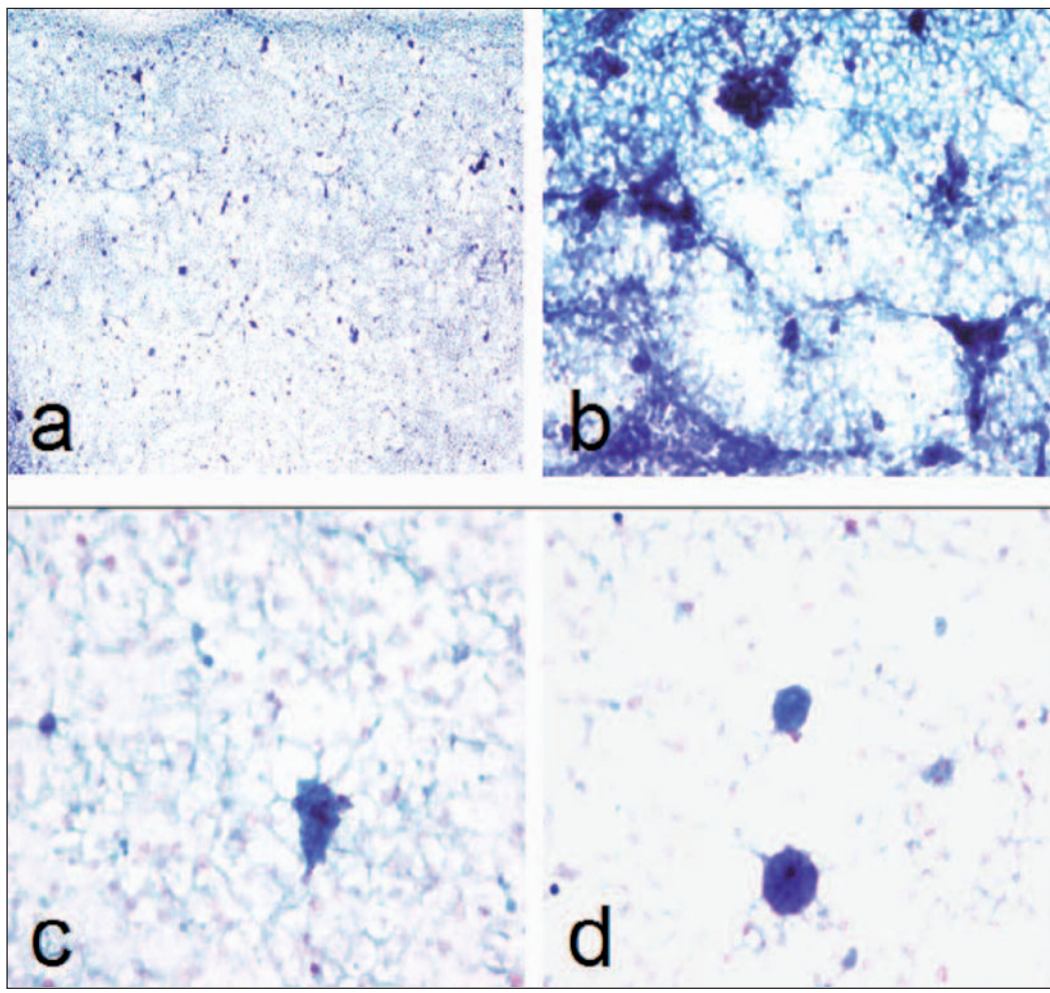


**FIGURE 1:** Dirty, necrotic background, numerous histiocytes, a few ductal epithelial cells and inflammatory cells (PAP EA-50, x40, x100, x200, x400).
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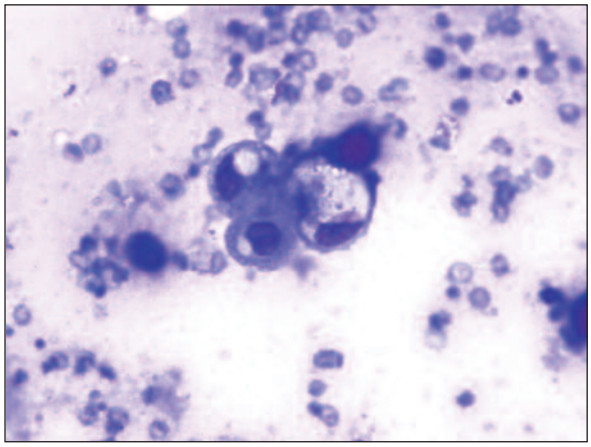

**FIGURE 2:** Atypical cells with hyperchromatic nuclei and cytoplasmic granules and vacuoles that led to the strong suspicion of malignancy, sometimes forming three dimensional clusters (Giemsa, x400).
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lignancy" together with the clinical features. The patient underwent simple mastectomy. Frozen section showed large areas of necrosis, solid areas of apocrine cells, the cells which could not be exactly defined, and histiocytes. The diagnosis was reported as malignant and the presence of apocrine cell groups and large areas of necrosis was noted. The patient was considered to be at Stage 4 clinically and a simple mastectomy was performed.

In macroscopic evaluation it was found that, a mass lesion which filled all quadrants of the breast and measured 10.5x8.5 cm, with scattered areas of cystic degeneration, retraction and discharge, ulceration of the breast skin. The great majority of the tumor was necrotic (Figure 3 a,b). Histopathological examination revealed a neoplastic infiltrating carcinoma consisting of adenoid and papillary formations in a desmoplastic stroma, and large areas of necrosis. The carcinoma consisted of apocrine cells with huge and vesicular nuclei, prominent nucleoli and abundant eosinophilic granular cytoplasm (Figure 4 a-d). Apocrine carcinoma was diagnosed based on these findings. Immunohistochemical examination of the neoplastic cells was positive for gross cystic disease fluid protein-15 (GCDFP-15). Hormonal receptors (ER and PR) were negative. Tumor cell membranes were negative for C-erb-B2. Moreover, Bcl-2 was negative, and there was a nuclear positivity rate of 8% for Ki 67 and p53.

## DISCUSSION

Apocrine carcinoma is a rare breast carcinoma. Takeuchi and colleagues reported an incidence of 1.6% of apocrine carcinoma in a series of 2091 pri-

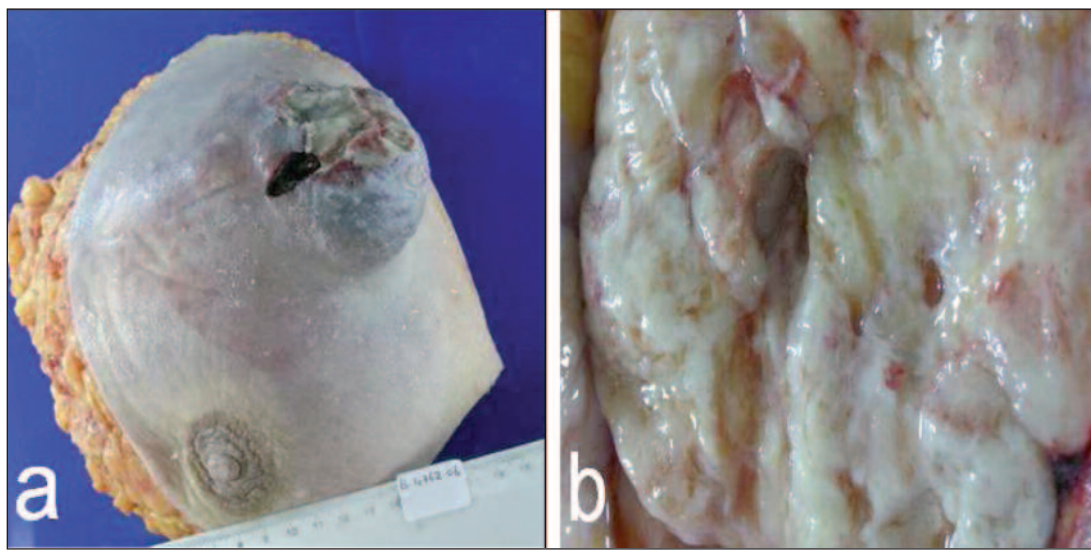


**FIGURE 3:** Gross description: **a)** Macroscopic examination revealed a mass lesion, retraction and discharge, ulceration of the breast skin. **b)** A mass lesion which filled all quadrants of the breast and measured 10.5x8.5 cm, scattered areas of cystic degeneration.
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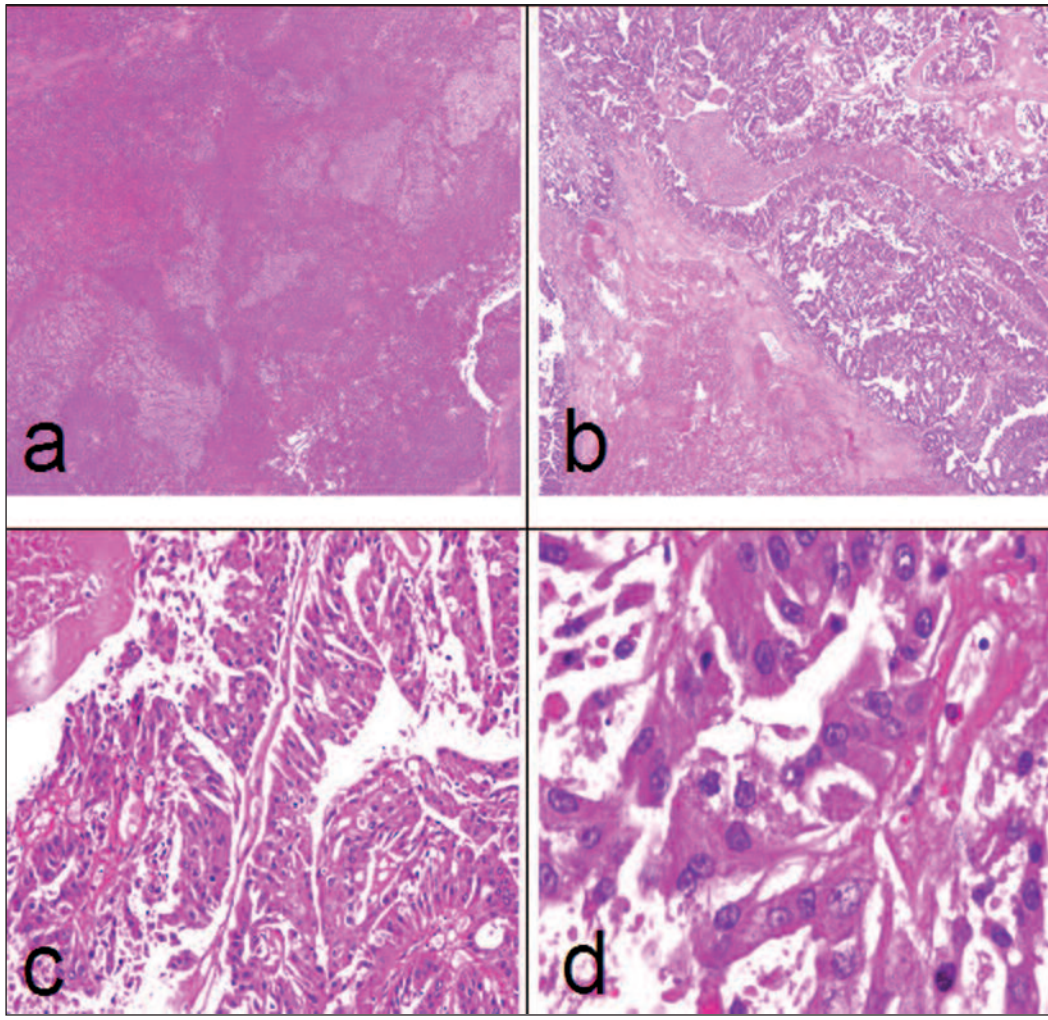


**FIGURE 4:** A tumoral parenchyma consisting of adenoid and papillary invasions into the thin desmoplastic stroma with solid layers of distinct size beside the large necrosis areas, and the tumor consisted of apocrine cells with huge vesicular nuclei, prominent nucleoli and large eosinophilic cytoplasms (hematoxylin and eosin, x40, x100, x200, x400).
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mary breast carcinomas.[3] It is suggested that prognostic factors of invasive apocrine carcinomas are similar to invasive ductal carcinomas, and the patients have prolonged survival with less aggressive prognosis, when tumoral staging and axillary involvement is considered.[6] Furthermore, there are some reports suggesting that the recurrence and survival rates are similar in both two condition.[3]

There are no obvious differences between apocrine carcinomas and invasive ductal carcinomas regarding clinical presentation and radiological imaging.[7,8] Groups of calcification that can reflect a benign view may be seen in apocrine tumors.[9] Mammographic imaging revealed peripheral macrocalcifications with central cystic areas that filled the whole left breast in our case.

It is usually difficult to diagnose apocrine carcinoma preoperatively. The differential diagnosis of apocrine carcinoma should be made and apocrine carcinoma should be distinguished from benign apocrine lesions and other eosinophilic and granular cell tumors on FNAC. Generally, by cytological examination, there are some cells with sparse groups consisting of hyperchromatic nuclei and large polygonal eosinophilic cytoplasm. These cells can be seen either in benign lesions such as

atypical apocrine adenosis, apocrine adenoma, granular apocrine metaplasia, and granular histiocytes owing to degenerative cyst and radial scar, or in malignant lesions such as mucinous carcinoma and ductal carcinoma (Table 1).[10] Johnson et al. reported that apocrine metaplastic cells were very often seen in FNAC of breast lesions, mainly in fibrocystic disease and those apocrine cells could be atypical and lead to difficulties in the diagnosis.[11] They also reported that in contrast to sparse distribution, huge and atypical nuclear status of apocrine carcinoma, apocrine cells in benign lesions such as atypical apocrine adenosis, apocrine adenoma, granular apocrine metaplasia, and degenerative cyst were round and uniform and formed more regular layers.[11] Apocrine cancers, as also seen in our case, are positive for GCDFP-15 with a high ratio. Honma et al. showed that the tumor was stained well (75%) with GCDFP-15, while ER, PR, and Bcl-2 expressions were very low (3.8, 5.8, and 1.9%, respectively).[2] Similarly, our case was widely positive for GCDFP-15 while E, PG, and Bcl-2 receptors were negative.

Apocrine cells and oncocytes share similar morphologic features at the hematoxylin-eosin level; however, there are some differences that allow a confident distinction between these two cell types. Mitochondria in apocrine cells are usually in a perinuclear location and are not so numerous and diffusely dispersed as in oncocytes. In addition, apocrine cells display features of active secretory elements: prominent microvilli, well-developed Golgi complex, and electron dense secretory granules polarized toward the luminal pole. GCDFP-15, as a typical marker of apocrine differentiation, was positive in our case, on the other hand, the same marker was negative in the oncocyte cells.[12]

Matsuo et al. classified the apocrine breast tumor into three subgroups histopathologically.[13] According to these authors, type I is intraductal enlarging type, type II is associated with adenosis, and type III is the infiltrating type. Lymph node metastasis is not seen in type I and II and the prognosis is favorable. Type III has lymph node metastasis and shorter survival. The authors also reported that apocrine carcinomas were often seen in older patients and microcalcifications were uncommon, although tumoral shadow was obtained on mammography. According to that classification, our case was type III.

**TABLE 1:** The differential diagnostic features of apocrine lesions of breast.

| Apocrine malignant lesions | Apocrine benign lesions |
|---|---|
| Apocrine carcinoma | Apocrine adenosis |
| Secretory carcinoma | Apocrine adenoma |
| Histiocytoid carcinoma | Granular apocrine metaplasia |
| Lipid rich carcinoma | Granular histiocytes |
| Oncocytic carcinoma | Degenerative cyst |
| Mucinous carcinoma | Radial scar |
| Ductal carcinoma | Fibrocystic disease |

Consequently, apocrine breast carcinoma is an entity that is rarely seen among the entire group of breast cancers. It is obvious that cytological and histopathological examinations are necessary when there is clinical and radiological suspicion, considering the wide benign and malignant spectrum of apocrine lesions of the breast. As in our case, during the examination of the preparations of a low cellular FNAC of a breast lesion with large areas of necrosis, the differential diagnosis of atypical apocrine adenosis, granular apocrine metaplasia, granular histiocyte owing to degenerative cyst and radial scar should be taken into account and an incisional biopsy should be considered. As a result, clinical follow-up should be performed with necessary surgical treatment and definite histopathological determination, and contribute to the prognosis.

The apocrine metaplastic cells are frequently seen in the FNAC of the breast lesions , and constitute a feature that may complicate the diagnosis of many lesions, such as fibrocystic disease. It should not only be considered mainly in the diagnosis of benign lesions such as apocrine adenoma, atypical apocrine adenosis, and granular apocrine metaplasia, but also in the preoperative cytologic diagnosis of apocrine carcinoma.

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