

## Low grade intraductal breast carcinoma with apocrine features as a precursor of infiltrating apocrine carcinoma

### Carcinom mamar intraductal de tip apocrin cu grad jos de malignitate - precursor al carcinomului mamar apocrin infiltrativ

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#### Abstract

*A 50-year old patient was referred to the Department of Radiology for an annual screening mammogram. Radiologically, a non-palpable right breast lesion with microcalcifications was located in the upper external quadrant. On light microscopy, two adjacent but different lesions were identified that were both associated with apocrine adenosis, radial scar and proliferative fibro-cystic disease. The two areas of 8 respectively 10 mm diameter consisted of apocrine ductal carcinoma in situ (ADCIS) of low grade that intimately merged with distorted and compressed small clusters or tubules of apocrine cells with low grade nuclei and large amount of eosinophilic granular cytoplasm. However, these clusters lacked myoepithelial cells on both microscopic and immunohistochemical examinations and consecutively were interpreted as infiltrating areas of well differentiated apocrine carcinoma (AC). In this case, where small sized multifocal low grade infiltrating AC developed on a complex background of apocrine adenosis and sclerosing lesion, immunohistochemistry was instrumental in order to establish the absence of myoepithelial cells. Similar to other types of infiltrating carcinomas, low grade infiltrating AC may develop from low grade ADCIS, since both lesions have similar morphological and immunohistochemical profiles.*

**Key words:** apocrine infiltrating carcinoma, apocrine in situ carcinoma, complex sclerosing apocrine lesion, breast

#### Rezumat

*Prezentăm cazul unei paciente de 50 de ani care s-a adresat Departamentului de Radiologie pentru o mamografie anuală identificându-se astfel o leziune nepalpabilă asociată cu microcalcificari și localizată în cadranul supero-extern al sânului drept. A fost efectuată sectorectomie iar la examenul microscopic al piesei operatorii au fost identificate două leziuni adiacente, ambele asociate cu adenoză apocrină, cicatrice radială și mastopatie fibrochistică proliferativă. Cele două arii cu diametrul de 8, respectiv de 10 mm erau constituite din*

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*focare de carcinom ductal in situ de tip apocrin cu grad jos de malignitate înconjurate de cuiburi și structuri tubulare mici, cu arhitectura distorsionată de prezența ariilor de hialinizare stromală și constituite din celule apocrine, cu nuclei cu grad jos de malignitate și citoplasmă abundentă eozinofilă, granulară. Aceste cuiburi nu sunt înconjurate de celule mioepiteliale, infiltrază stroma și au fost interpretate ca arii de carcinom apocrin infiltrativ bine diferențiat. În acest caz, unde un carcinom apocrin infiltrativ cu grad jos de malignitate multifocal de dimensiuni reduse s-a dezvoltat pe un fond complex de adenoză apocrină și leziune sclerozantă, examenul imunohistochimic a fost determinant în demonstrarea absenței celulelor mioepiteliale. Similar cu alte tipuri de carcinom infiltrativ, carcinomul apocrin infiltrativ cu grad jos de malignitate se poate dezvolta dintr-un carcinom in situ de tip apocrin cu grad jos de malignitate, ambele leziuni având un profil morfologic și imunohistochimic similar.*

**Cuvinte cheie:** *carcinom apocrin infiltrativ, carcinom apocrin in situ, leziune complexă sclerozantă apocrină, glandă mamară*

## Introduction

Apocrine changes or metaplasia are often seen in a wide spectrum of breast lesions that encompass normal looking ducts or acini, benign cysts and in situ or infiltrating neoplasms. Most of them are easily diagnosed while others are challenging, especially when atypia is found. Criteria to distinguish apocrine atypia from low-grade or high-grade DCIS often emphasize cytological features rather than architecture (1, 2), thus making their interpretation even more difficult.

We present a case of a small size multifocal infiltrating low grade AC, associated with atypical apocrine adenosis and low grade ADCIS, that originated in a complex sclerosing lesion. The abundant hyaline matrix and distortion of the small neoplastic glands made the identification of the myoepithelial cells difficult, even after performing an extensive immunohistochemical study.

This case may exemplify a model of tumor progression for apocrine infiltrating carcinoma similar to other types of infiltrating carcinoma of the breast, where both low grade infiltrating carcinomas arise from a low grade lesion (DCIS) and a high grade ones originate from a high grade precursor.

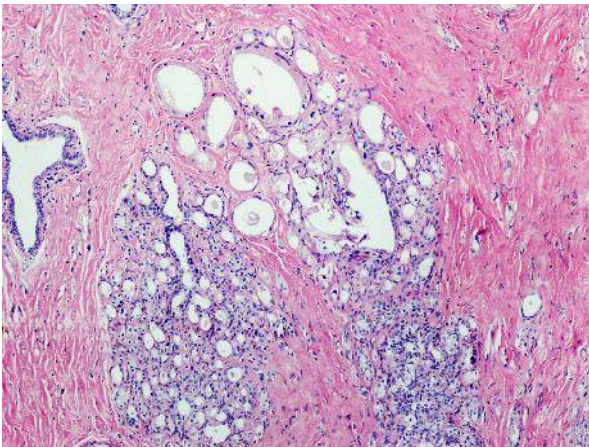
## Case report

A 50-year old patient was referred to the Department of Radiology for an annual

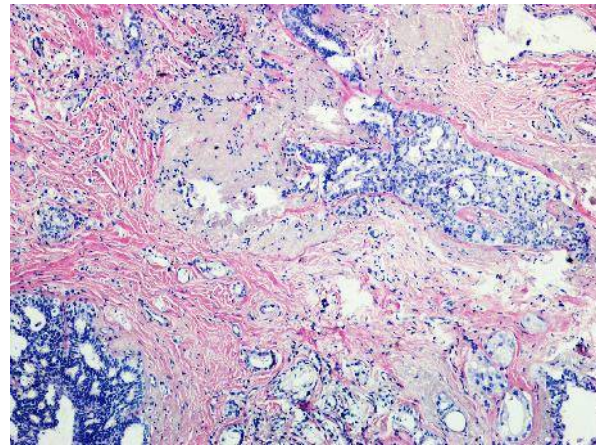
mammography screening, where a non-palpable right mass of the upper-external quadrant was highlighted by the presence of microcalcifications and finally considered suspicious for malignancy (BIRADS 5). Ultrasound examination revealed a 20 mm architecturally distorted area, associated with multiple 3-5 mm diameter cysts. Right upper external quadrantectomy was initially performed.

On macroscopic evaluation, the lesion was firm and poorly delineated, white-tan on cut section and contained multiple small cysts. It involved the lateral resection margin and was surrounded by extensive fibrotic tissue containing cysts, some of up to 10 mm, with serous fluid content.

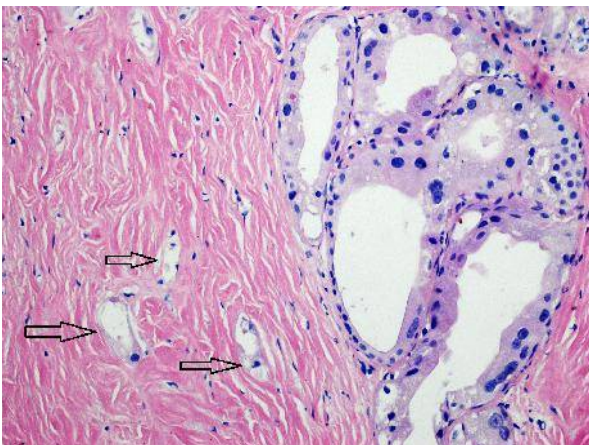
Microscopically, there were two distinct lesions measuring 8/6 mm and 10/7 mm surrounded by complex sclerotic changes and proliferative fibro-cystic disease, with the smaller one involving the lateral resection margin. The two lesions had the same microscopic appearance and were separated by 5 mm of fibrotic tissue. The main morphologic changes were represented by nodular atypical apocrine adenosis (*Figure 1*). They were in close relation with areas of radial scar (*Figure 2*). Isolated, small clusters or tubules of atypical apocrine cells were seen around these cystically dilated structures (*Figure 3*). They were compressed and distorted by the surrounding hyalinized stroma that obscured the presence of myoepithelial cells (*Figure 4*). Apocrine cells exhibiting low grade nuclei and large amount of eosinophilic granular cytoplasm were diffusely



**Figure 1. Enlarged lobule with increased number of ductules and acini associated with prominent apocrine atypical metaplasia**



**Figure 2. Radial scar with central fibroelastotic area surrounded by ducts and acini with or without intraluminal proliferation**



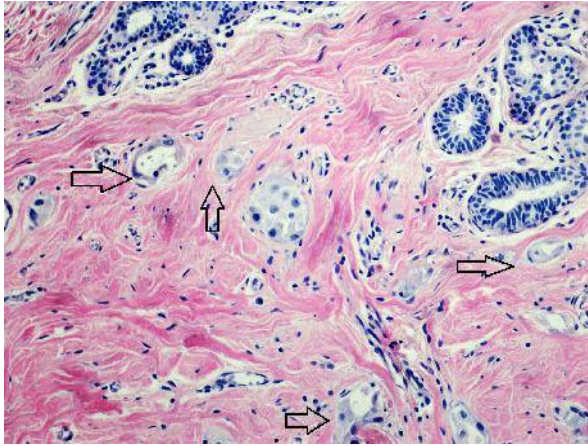
**Figure 3. Small tubules of atypical apocrine cells are seen in the vicinity of dilated structures with atypical apocrine proliferation**

positive for high molecular weight cytokeratin 34 $\beta$ E12 and negative for CK 5/6. Myoepithelial markers such as CD10, actin and p63 were constantly negative (Figure 5). However, apocrine cells had a confusing and uncharacteristic p63 cytoplasmic positivity while the compressed stromal myofibroblasts had actin positive cytoplasm. These areas were interpreted as a well differentiated infiltrating AC. They were negative for estrogen receptors (ER) and positive for progesterone

receptors (PR), which were present in 60% of the tumor cells. The HER2 score was 1+. Areas of grade 1 intraepithelial lobular neoplasia were observed both at the periphery of the two infiltrating lesions and in the surrounding breast tissue.

In addition to the atypical apocrine adenosis and radial scar, small or large dilated cysts lined by two layers of external myoepithelial and internal flat apocrine epithelium were found at the periphery of both infiltrating areas. The apocrine cells had large amounts of granular eosinophilic cytoplasm and large but mildly pleomorphic nuclei. Other apocrine cysts were lined by atypical cells forming micropapillae that eventually fused to form cribriform spaces. They were positive for CK34 $\beta$ E12 but negative for CK 5/6, the latter one having a mosaic pattern in the surrounding cysts with non-atypical intraepithelial non-apocrine proliferation. Staining for the ERs was negative in this intraductal atypical apocrine proliferation but PRs were positive in 70% of the cells. HER-2 score was analogous to the infiltrating lesions. This pattern was consistent with low grade ADCIS.

Microcalcifications were seen in normal acini and in areas of apocrine adenosis, low grade ADCIS and infiltrating carcinoma.



**Figure 4. The hyalinised stroma compresses the tubular apocrine structures obscuring the presence of myoepithelial cells**

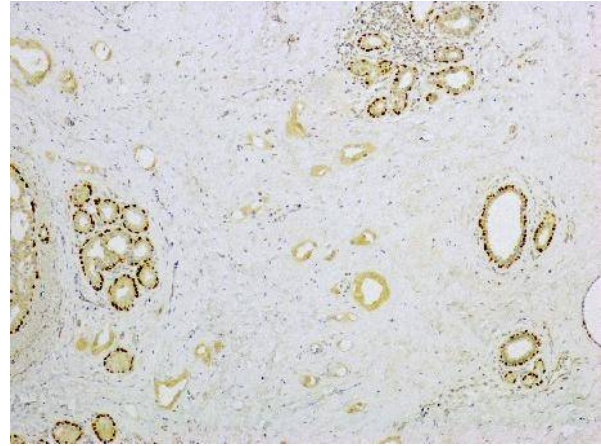
Because of the positive resection margin, the patient underwent a complete mastectomy with axillary lymph node dissection. After extensive sampling of the definitive surgical specimen, no residual disease was identified and 10 axillary lymph nodes were uninvolved by tumor.

The patient underwent 6 cycles of chemotherapy and is now well and free of disease, 2.5 years after the initial diagnosis.

## Discussion

Breast apocrine changes (or metaplasia) are a very common finding and contain cells with an eosinophilic granular cytoplasm, large vesicular nuclei with prominent eosinophilic nucleoli and occasional presence of apical snouts. They can be present in a wide range of benign lesions that includes apocrine cysts, fibroadenoma or papilloma and lesions in which apocrine changes are associated with atypia. The ones that are not associated with atypia have a low risk of subsequent carcinoma development while those associated with atypia have an increased risk (*Table 1*).

Problems and heterogeneity of apocrine lesions have been identified when defining AD-



**Figure 5. The p 63 marker revealed the absence of myoepithelial cells around the apocrine tubules infiltrating the stroma**

CIS in contrast to apocrine atypia. The main criteria to define these three lesions emphasize cytological features rather than architecture and are shown in *Table 2* (1, 2, 9).

Initially, most papers published failed to show whether low grade ADCIS has a different clinical behavior and prognosis from high grade DCIS. According to the proposed grading system for ADCIS, 28.6% of non-infiltrating lesions could have been graded as low grade in the study of Leal and colleagues (9). Of these, 2 cases were associated with invasive carcinoma, however, the authors did not mention which type and grade the infiltrating component was in these cases. They also found that low grade ADCIS has the same DNA content as high grade ADCIS, Ki-67 and c-erb-B2 expression were similar, and there are other substantial molecular data to conclude that these lesions can behave aggressively and can be a precursor of infiltrating carcinoma (9, 10).

There is convincing genetic evidence to suggest that low grade, high grade DCIS and invasive breast cancers evolve through distinct evolutionary pathways, so that a new dual theory has been proposed concerning the origin of infiltrating breast carcinomas (11). On the basis of these concepts, related high grade infiltrating

**Table 1. Morphology and risk of recurrence in various lesions associated with apocrine metaplasia**

Type of lesion	Morphology	Risk of carcinoma development	References
Single or multiple cysts with apocrine epithelium	More than 1 cm diameter	0- 3	(3, 4, 5, 6)
	Micropapillary or cribriform architecture, no atypia	1.4-3	(7)
Fibroadenoma or papilloma	Focal apocrine changes without atypia	0	(1)
Apocrine atypia in various breast mass-forming lesions	Threefold nuclear enlargement, enlargement of nucleoli	5.5 (14 in patients over 60 years old)	(8)

**Table 2. The main criteria to define apocrine atypia, low grade ADCIS and high grade ADCIS**

Type of lesion	Morphologic criteria
Apocrine atypia	Both nuclear and nucleoli enlargement; fine chromatin; less than 25% of cells with apocrine atypia; no cribriform or micropapillary architecture; necrosis not present; size of lesion less than 4 mm that involves less than 2 lobular units
Low grade ADCIS	Irregular nuclear membranes and coarse chromatin in addition to nuclear enlargement; nuclear atypia present in more than >25% of cells; necrosis not present; apoptosis may be observed; cribriform architecture; more than 4 mm in size and involves more than 2 lobular units
High grade ADCIS	Multiple prominent nucleoli, irregular nuclear membrane, coarse chromatin, nuclear enlargement; comedo-type necrosis is present

carcinomas show a high grade precursor while low grade ones exhibit a low grade one. The present case shows that this model of progression can also occur in apocrine infiltrating carcinomas, since the low grade infiltrating lesion was only associated with a corresponding low grade DCIS. Moreover, this is suggested by the similar immunoprofile of both neoplastic lesions which were ER- negative, PR- positive and had a HER2 1+ score.

There are few reports concerning the diagnosis of low grade infiltrating AC, especially of small size multifocal cases. When this lesion develops on a background of complex sclerosing changes with apocrine adenosis with atypia and low grade ADCIS, the diagnosis is difficult since the abundant hyaline material deforms the tubular architecture of malignant areas, distorting its infiltrative features. Even when not atypical,

apocrine adenosis involving sclerosing lesions can impart a worrying cellular morphology that, when accompanied by stromal fibrosis and architectural distortion, may resemble a malignant lesion. The benign or malignant nature of these biopsies, however, is readily appreciated by demonstrating the abundance of myoepithelial cells positive for various immunohistochemical markers, however bearing in mind that none of them is fully specific (12).

When considering the differential diagnosis, the fact that some of the benign apocrine glandular structures of the breast may lack myoepithelial cells must be taken into account (13). In these cases, the use of two or more immunohistochemical markers is advisable, preferable associating a nuclear marker (p63) for cases in which the cytoplasm of the myoepithelial cells is compressed and a cytoplasmic marker for the cases where cells have a

swollen cytoplasm. However, sometimes the cytoplasm of benign or malignant apocrine cells can be positive for p63 or other myoepithelial markers; Kalof et al. documented focal staining of luminal epithelial cells of normal ductal epithelium and a consistent staining of the luminal surfaces of apocrine metaplastic cells with such markers (14). In our case, p63 was completely negative around the suspicious tubules but the cytoplasm of the epithelial atypical apocrine infiltrating cells was positive for p63. The only other breast benign lesion lacking myoepithelial cells is microglandular adenosis. However, the apocrine malignant lesion described in this case was small, multifocal and certainly did not share a microglandular architecture. Moreover, the characteristic intraluminal secretion is also absent whereas the apocrine features were present.

Androgen receptors have been shown to be positive in benign apocrine cells while ERs and PRs are negative in both benign apocrine cells and apocrine in situ or infiltrating carcinomas. Still, some studies demonstrate a positivity of the latter ranging between 3 to 60% of the tumor cells in both type of lesions (15, 16). HER-2 overexpression has been reported in both benign and malignant apocrine lesions, ranging from 10 to 50% positivity, being lower in low grade ADCIS (17). In our case, both in situ and invasive low grade apocrine carcinomas have shown positivity for PRs with a 1+HER2 score. This shows that both in situ and invasive apocrine carcinoma have a heterogeneous immunohistochemical profile.

## Conclusions

The present case shows that low grade AC may develop from a corresponding low grade ADCIS and supports a dual theory of progression similar to that proposed for infiltrating ductal carcinomas.

When a small low grade infiltrating AC develops on the background of complex sclerosing lesion associating apocrine adenosis, immunohistochemistry is instrumental to prove the lack of myoepithelial cells.

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