

# Expression of hormone receptors in low-grade adenosquamous carcinoma of the breast

## A case report

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### Abstract

**Rationale:** Low-grade adenosquamous carcinoma (LGASC) is a rare subtype of metaplastic breast carcinoma which is generally recognized as a characteristic subgroup of triple-negative breast cancers previously. However, in this study, we reported for the first time a case of LGASC with hormone receptors expression.

**Patient concerns:** Pathological analysis of breast tumor specimen obtained by a 42-year-old female patient was performed. Morphologically, it composed of glandular structures with scattered squamous differentiation accompanied by haphazard arrangement of spindle cell stroma. Immunohistochemically, all myoepithelial and squamous differentiation markers showed typical LGASC positive or negative staining pattern. Interestingly, we found that normally aberrant hormone receptors were reactivated in this case. To our knowledge, this is the first report of a hormone receptor-positive LGASC. Apart from this, in the extended resection sample, we found scattered squamous metaplasia and florid adenosquamous proliferation (ASP). Meanwhile, it was positive for CD44 variant isoforms (CD44v), which is a breast cancer stem cell (CSC) marker, and expressed in LGASC, squamous metaplasia, and ASP.

**Diagnosis:** LGASC with hormone receptors expression.

**Interventions:** The breast-extended local excision and axillary lymph node dissection were performed.

**Outcomes:** The patient was free of local recurrence and distant metastasis 6 months after surgical resection.

**Lessons:** We herein report the first case of LGASC with immunoreactivity for hormone receptors, expanding its profile of immunophenotypes. CD44v may play an important role in the transition of LGASC precursor lesions into malignant processes, which may serve as a therapeutic target in LGASC.

**Abbreviations:** ASP = adenosquamous proliferation, CD44 v = CD44 variant isoforms, CK 5/6 = cytokeratin 5/6, CK 7 = cytokeratin 7, CSC = cancer stem cell, ER = estrogen receptor, HER2 = human epidermal growth factor receptor 2, LGASC = low-grade adenosquamous carcinoma, MBC = metaplastic breast cancer, PR = progesterone receptor, RSL = radial sclerosing lesion, SMA = smooth muscle actin.

**Keywords:** breast, CD44 variant isoforms, estrogen receptor, low-grade adenosquamous carcinoma, metaplastic breast cancer, progesterone receptor

## 1. Introduction

Metaplastic breast carcinoma (MBC), accounting for <1% of all breast cancers, is a rare heterogeneous malignant group.<sup>[1]</sup> Morphologically, MBC is characterized by various combinations of adenocarcinoma, sarcomatoid, and other epithelial components. Till 2000, it was recognized as a distinct pathologic entity

by the World Health Organization.<sup>[1]</sup> Due to its rarity, many aspects of MBC, including its morphological and immunohistochemical profiles, remain unclear. Generally, MBC has a low positivity for hormone receptors (estrogen and progesterone receptors), and shows limited expression of human epidermal growth factor receptor 2 (HER2) protein.<sup>[2]</sup> Most of MBC cases are classified as high-grade lesions, whereas a low-grade variant, such as the low-grade adenosquamous carcinoma (LGASC), has also been reported.<sup>[3]</sup> LGASC is characterized by well-developed tubule formation intimately admixed with solid nests of squamous cells in a spindle stromal cell background. Although, LGASC can occasionally express HER2,<sup>[4]</sup> no hormone receptor case has been reported. We herein present a case of estrogen receptor (ER) and progesterone receptor (PR)-positive LGASC, and explore its possible pathogenesis. To our knowledge, this is the first case report of LGASC with hormone receptor staining.

## 2. Case report

A 42-year-old female presented with a palpable mass lesion in the upper outer quadrant of her right breast. Through sonographic examination, a size of 1.5 cm × 1.4 cm mass with sharply defined borders was found (Fig. 1). Color Doppler ultrasonography was used to visualize the blood flow signal in and around the mass. A short rod-like blood flow was seen at the margin of the mass, but

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there was no obvious color flow signal in the interior. There were no risk factors for breast cancer, and also no significant family history of breast/ovarian cancer from this patient. Physical examination showed no evidence of nipple discharge and skin changes. There were no remarkable findings in the left breast parenchyma and both axillary areas. Resection was done to the right breast mass at local hospital. Two months after the mass resection, the breast-extended local excision and axillary lymph node dissection were performed in our hospital.

The removed tissue was fixed in 10% neutral-buffered formalin for pathological study. Histopathologically, the mass has relatively clear border, except for some focal infiltrations (Fig. 2A). It was morphologically composed of glandular structures with scattered squamous differentiation, and also a haphazard manner of arrangement of spindle cell stroma. The contours of glands ranged from round to irregular, which fused with the collagenous stroma. Because of the well-differentiated appearance, some neoplastic glands were indistinguishable from normal glands. Mitotic activity was uncommon, and clusters of lymphocytes were observed at the periphery of lesion.

To better understand the tumor components, immunohistochemical stainings were performed using the ChemMate Envision

method (DakoCytomation, Glostrup, Denmark). Myoepithelial markers including p63, p40, Calponin, SMA, and CK5/6 showed a spectrum of complete, discontinuous, or absent staining around lesional glands, respectively, which is showed in Fig. 2B and C. Squamous differentiation was also highlighted by p63, p40, and CK5/6. CK7 was intensely expressed in the luminal epithelial cells (Fig. 2D). p53 was expressed in less than 10% of nuclei. Reactivity of cathepsin D was found in myoepithelial and squamous differentiation. Surprisingly, the luminal epithelial cells also exhibited ER (Fig. 2E) and PR (Fig. 2F) strongly and diffusely. However, the expression of HER2 was not detected in the lesional glands. In addition, both myoepithelial and squamous differentiation showed positive membranous expression of CD44 variant isoforms (CD44v) (Fig. 2G). The Ki-67 labeling index was 10% in high density tumor area.

Microscopic examination of the extended resection sample revealed no tumor remnants. However, scattered squamous metaplasia (Fig. 3 A) with papilloma and adenosquamous proliferation (ASP) (Fig. 3B) were observed. Both the squamous metaplasia and the myoepithelial of ASP showed positivity for CD44v (Fig. 3C, D).

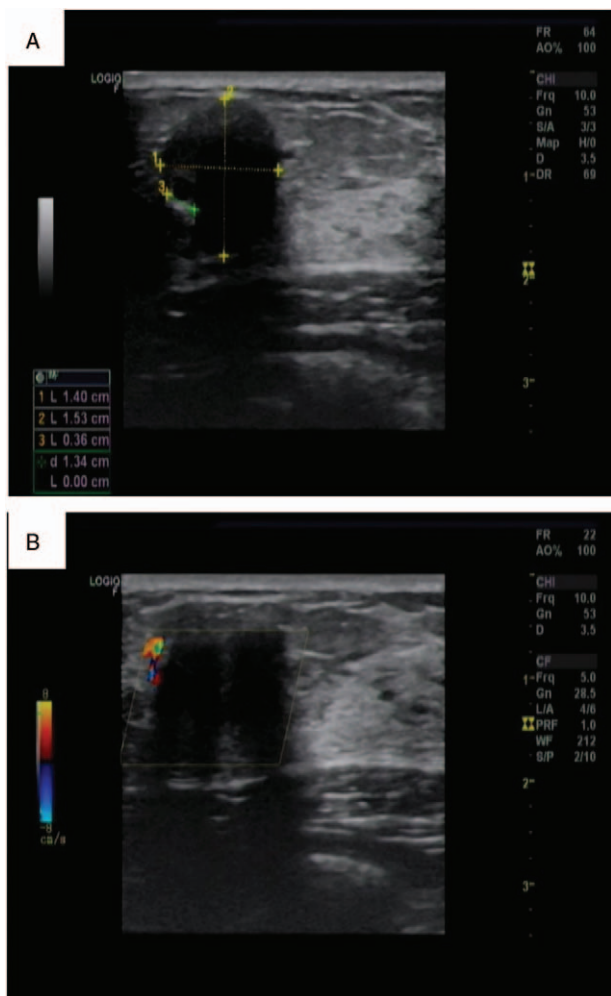
Ethical approval was not applicable for this case report as it did not involve any human trials or the patient's privacy. Informed consent was provided by the patient for the publication of this case report.

### 3. Discussion

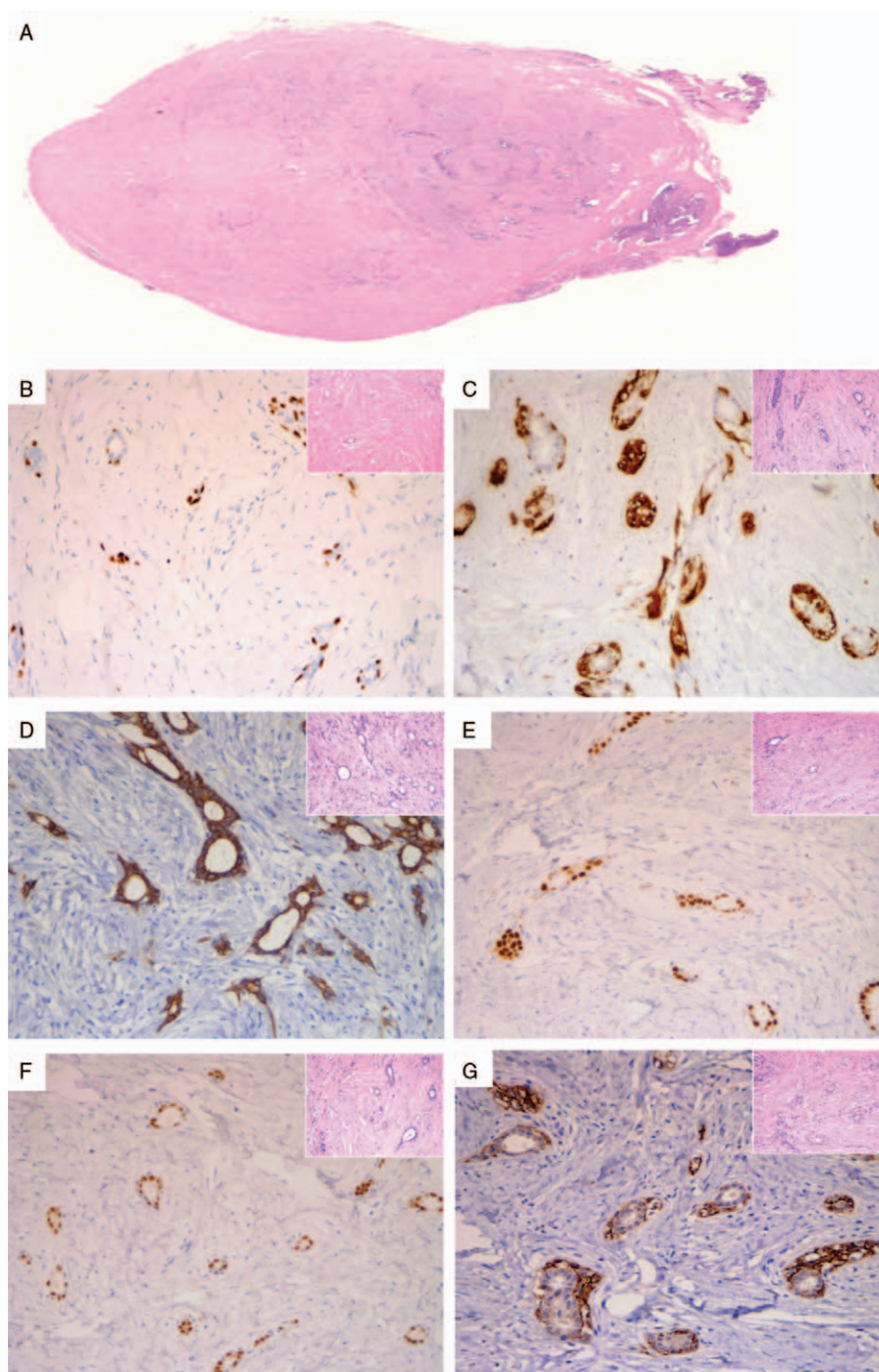
Low-grade adenosquamous carcinoma is a rare histological type of breast cancer, characterized by its low-grade nature. Currently, the WHO classifies LGASC under "MBC." Clinically, LGASC can occur in any age resembling the conventional invasive carcinoma of no special type of component.<sup>[5,6]</sup> It always presents as a palpable breast mass while bilateral lesions have also been reported.<sup>[7]</sup> Although mammographic and sonographic imaging is nonspecific for LGASC, raising suspicion may lead to subsequent biopsy.<sup>[3]</sup> Due to the lack of malignant cytological features and overall architecture, preoperative confirmation is extremely difficult.<sup>[8,9]</sup> Because of limited sampling and processing artifacts, intraoperative frozen section consultation was also challenging.<sup>[3,9]</sup>

Histologically, infiltrative growth of deceptively bland-looking epithelial cells is observed in breast parenchyma. Surrounding myoepithelial components are easily found in the tumor, which can be confused as normal luminal epithelial and basal myoepithelial mammary structures and may lead to misdiagnosis as a benign tumor.<sup>[5,9]</sup> The low-grade cytomorphology was also histological correlates of indolent clinical behavior. Tumor cells show variable amounts and degrees of squamous differentiation, whereas the spindle stromal cells often appeared to merge with the epithelial cells.<sup>[7]</sup> Clusters of lymphocytes were also observed at the periphery. LGASC was always accompanied by the adenomyoepithelioma, intraductal papilloma, and sclerosing proliferative lesions in the tumor around.<sup>[10]</sup>

Immunohistochemically, both myoepithelial and luminal epithelial markers were variably expressed in LGASC.<sup>[11]</sup> The phenomenon that myoepithelial markers showed complete, discontinuous, and absent patterns were deemed uniquely in LGASC,<sup>[3,11]</sup> which could be observed in our case. Classically, LGASC displayed a triple-negative immunophenotype.<sup>[5]</sup> However, Drudis et al<sup>[4]</sup> reported that HER2 was found in glandular elements of 46% of the tumors, indicating the heterogeneity in the expression profiles of LGASC. Here, we firstly report the



**Figure 1.** Imaging studies using sonographic examination. (A) Ultrasonography showing an oval-shaped hypoechoic mass, 1.5 cm in size, located in the upper outer quadrant of right breast. (B) Visualization of the blood flow signal in and around the mass using color Doppler ultrasonography.

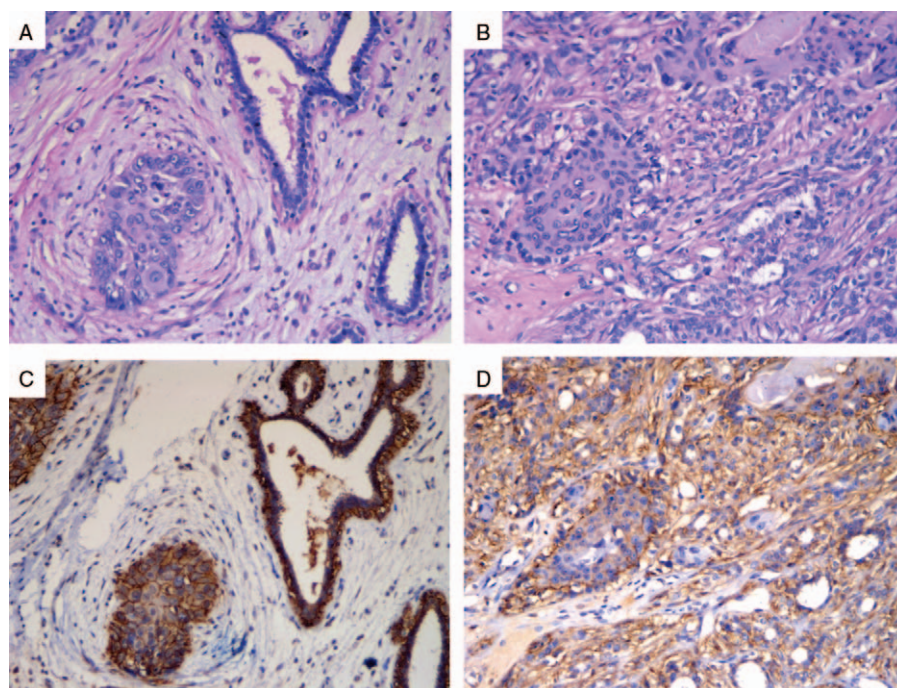


**Figure 2.** Pathological findings of low-grade adenosquamous carcinoma (LGASC). (A), Hematoxylin-eosin section of the whole appearance of the lesion. p63 (B) and Calponin (C) expression with a spectrum of complete, discontinuous or absent staining around lesional glands. CK7 (D), ER (E) and PR (F) expression by the luminal epithelial cells of LGASC. CD44v (G) expression by myoepithelial and squamous differentiation of LGASC. The image magnification of Fig. B-G are  $\times 200$ .

expression of hormone receptors in LGASC, while the exact reason remains unclear. In rare cases, recurrence adenosquamous carcinoma of breast is invasive ductal carcinoma with ER and PR expression,<sup>[12]</sup> it could be that adjuvant chemotherapy alters the hormone receptor status.<sup>[13]</sup> In addition, it was reported that hormone receptors can regulate the expression of CD44v, which is considered having correlation with cellular differentiation in breast cancer.<sup>[14]</sup> The expression of CD44v is mainly restricted to myoepithelial cells in normal breast tissues.<sup>[15]</sup> In contrast, it can

express in a variety of breast cancer.<sup>[15-17]</sup> However, this had no reports of the CD44v expression in myoepithelial and squamous differentiation of LGASC previously. Furthermore, CD44v, a widely accepted cancer stem cell (CSC) marker in breast cancer, is considered to promote the tumor progression in various cancers.<sup>[18]</sup> As LGASC is proposed to arise from the myoepithelium,<sup>[19]</sup> we hypothesize that the high expression level of CD44v in LGASC might relate to the differentiation of the breast cancer stem cells to myoepithelial and squamous cells.





**Figure 3.** Pathological findings of squamous metaplasia and adenosquamous proliferation (ASP) in the extended resection sample. Hematoxylin-eosin section of squamous metaplasia (A) and ASP (B). CD44v expression by both the squamous metaplasia (C) and the myoepithelial of ASP (D). The image magnification of (A–D) is  $\times 200$ .

The etiology of LGASC is still unclear. LGASC always coexist with radial sclerosing lesion (RSL), fibroadenoma, phyllodes tumors, and adenomyoepithelioma.<sup>[7]</sup> It is reported that ASP associated with RSL may be a precursor of LGASC.<sup>[20,21]</sup> In the extended resection sample of our case, we simultaneously found squamous metaplasia and florid ASP, providing a hint that they were the potential precursors of LGASC. The squamous metaplasia and the myoepithelial of ASP were positive for CD44v, suggesting that CD44v might play an important part in the form of LGASC.

As a distinct subtype of MBC, the differential diagnosis should be performed to distinguish LGASC from benign fibrosclerosing lesions with squamous metaplasia, including radial scar/complex sclerosing lesion, syringomatous adenoma, myoid hamartoma, and pleomorphic adenoma without osseous or chondroid differentiation. Generally, LGASC is characterized by immunostaining in an inconsistent manner for various myoepithelial and cytokeratin.<sup>[11]</sup> Radial scar/complex sclerosing lesion is a benign lesion which can be mistaken for malignancy due to the attenuating myoepithelial cell layer. However, myoepithelial cell markers are present in radial scar/complex sclerosing lesion without an inconsistent pattern of expression like LGASC. Syringomatous adenoma of the nipple and LGASC have similar histological appearance and immunophenotype, which indicated that they may have a common origin.<sup>[19]</sup> But syringomatous adenoma locates in the nipple-areolar complex, whereas LGASC occurs within breast parenchyma. Myoid hamartoma is composed of varying amounts of smooth muscle cells, mammary ducts, lobules, fibrous tissue, and adipose tissue<sup>[22]</sup>; in contrast, LGASC does not contain smooth muscle cells. Squamous metaplasia can also be detected in breast pleomorphic adenoma (PA).<sup>[23]</sup> So when osseous or chondroid differentiation is lacking, it is difficult to distinguish between LGASC and PA. Although PA

is composed of epithelium and myoepithelial, myoepithelial staining patterns mentioned above are not likely to be seen in PA.

Low-grade adenosquamous carcinoma is a low-grade metaplastic carcinoma. Prognosis of LGASC was favorable, particularly compared with other metaplastic carcinomas. But local recurrence and rare axillary lymph node metastases were also reported.<sup>[3]</sup> Currently, LGASC has no consistent therapeutic strategy. Local excision with margins of 1 cm was recommended by some researchers.<sup>[5,7]</sup> Because of the rare lymph node metastasis, routine sentinel node biopsy or axillary clearance was not needed for patients with LGASC.<sup>[5]</sup> Six months after the operation, our case showed no local recurrence and distant metastasis.

#### 4. Conclusions

Low-grade adenosquamous carcinoma is a rare form of invasive breast carcinoma; the immunophenotypes of LGASC remain unclear. We report a case of LGASC with immunoreactivity for hormone receptors, expanding its profile of immunophenotypes. As a CSC marker of breast, CD44v may play an important role in the transition of LGASC precursor lesions into malignant processes, which may serve as a therapeutic target in LGASC.

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