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Low-grade adenosquamous carcinoma of the breast: a review with focus on imaging and management

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Abstract

Low-grade adenosquamous carcinoma is a less frequent variant of metaplastic breast carcinoma, incidentally detected during screening and has an age distribution similar to other breast carcinomas. It shares characteristics with both benign and malignant carcinomas: its mammographic and sonographic features are therefore nonspecific. Breast conserving surgery with adjuvant radiation therapy is currently the preferred therapeutic approach. The aim of this review is to describe the imaging and clinical features of low-grade adenosquamous carcinoma for appropriate identification and diagnosis. The associated pitfalls, histopathologic and epidemiologic factors, natural course, and management of low-grade adenosquamous carcinoma are also discussed.

Keywords

Low-grade adenosquamous carcinoma, metaplastic carcinoma, breast cancer

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Introduction

Low-grade adenosquamous breast carcinoma (LGASC) is a rare variant of metaplastic breast cancer histologically characterized by two coexisting components, a glandular one and a squamous one.[1,2] Adenosquamous carcinoma has been defined as a low-grade neoplasia; it is generally associated with local recurrences and only very rarely with metastases, although, in a few cases, evolution into a more aggressive form of metaplastic carcinoma was observed.[3]

LGASC of the breast was first described by Rosen and Ernsberger in 1987[4] and has since been reported occasionally in the literature. Later, Van Hoeven et al.[5] extended the clinical follow-up of the original series, added other cases and described the clinicopathological characteristics of LGASC.

As of now, LGASC belongs to the family of "metaplastic breast cancers"; this is a very heterogeneous group of tumors[6–8] with several microscopic grades and a different behavior and prognosis, accounting for <1% of overall breast cancers.[9] These tumors are triple negative breast cancers,[10] marked by squamous cells and/or mesenchymal-looking elements—including spindle, chondroid, and bone cells.[11]

Clinically, LGASC is most often asymptomatic but, less commonly, appears as a palpable mass.[4,12,13] Lesions are usually < 5 cm in diameter at diagnosis[12] and may be smaller if found on screening mammography.[13] Noel et al. reported a case of LGASC in a 49-year-old woman with BRCA mutation; because only few similar cases have been reported so far, it is more

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probable that LGASC was indeed an incidentaloma in a BRCA patient rather than having been caused by the mutation.[9] There are no specific findings on mammography and sonography; in fact, it shares features with both benign and malignant neoplasms. Most often, it appears as an architectural distortion on mammogram and an irregular hypoechoic mass with not circumscribed margins, indistinct or microlobulated, on ultrasonography (US).[14]

The optimal treatment strategy for LGASC is still unknown. Breast conserving surgery with adjuvant radiation therapy is today the preferred therapeutic approach to this cancer because of the very low incidence of nodal or distant metastases. Unlike the aggressive tumor behavior of other forms of metaplastic breast carcinomas, LGASC has an indolent course,[15] with a good long-term survival.[3,16] The aim of this review is to describe the imaging and clinical features of LGASC for appropriate identification and diagnosis. The associated pitfalls, histopathologic and epidemiologic factors, natural course, and management of LGASC are also discussed.

Pathophysiology features

Our review of the recent literature identified several theories on the pathogenesis of LGASC, mainly based on findings from small patient cohorts and/or anecdotal reports. Most notably, adenosquamous proliferation (ASP) associated with radial sclerosing lesion and papilloma may be a precursor of LGASC.[12,14] ASP in these lesions is usually viewed as benign squamous metaplasia with reactive hypercellular stroma, possibly secondary to infarction or previous core biopsy.

In other cases, LGASC may be due to metaplasia triggered by retained fragments of localization wires[17] made of stainless steel or nitinol (a metal alloy with approximately equal parts of nickel and titanium). Indeed, long-term exposure to metals may be associated with carcinogenesis, particularly for chromium and nickel which form complexes that lead to oxidative stress, inhibition of DNA damage repair, and alterations in gene expression.[18]

Demographic features

LGASC is an uncommon disease of the breast that can affect women aged 31–88 years.[5,13] It generally occurs in post-menopausal women and the average age ranges from 56 to 70 years,[2,5,14,19] although a case of LGASC has been reported in a woman as young as 19 years.[20]

In comparison with white women, black women were shown to have a higher incidence of getting LGASC[4]; however, LGASC is encountered worldwide in people of all races. Interestingly, the racial discrepancies in incidence are different from those of breast cancers in general, where the highest incidence is seen in white women.

Clinical manifestation

LGASC is usually asymptomatic and therefore incidentally found on screening mammography. Less commonly, for larger tumors, patients may present with a palpable mass[7,21] or breast tenderness. Lesions are generally <5 cm in diameter at diagnosis and may be smaller (0.7–3.0 cm, with an average size of 1.8 cm) if diagnosed during screening mammogram. Calcifications have also been reported in some patients.[14]

In a retrospective study of 10 women diagnosed with LGASC, the most frequent location was peri-areolar.[14] The nipple is rarely involved, with nipple changes such as retraction, ulceration, hardening, and secretions.[4,14]

LGASC is typically an unilateral lesion, with bilateral cases more rarely reported (1–9%). However, Wilsher and Snook reported bilateral carcinoma in up to 18% of cases.[21] The incidence of multiple synchronous (multifocal and multicentric) cancer is still not well defined in the literature.

Imaging findings

Imaging descriptions of LGASC are rare and limited to case reports and small case series.[9,12,14]

The preferred imaging strategies for the evaluation of LGASC are mammography and US, with a high-frequency linear transducer. In most cases, bilateral mammography involves taking two views of the breast (craniocaudal and mediolateral oblique), with subsequent additional views, if appropriate, for supplementary information or problem solving, for instance in the case of a focal asymmetry (Fig. 1). However, for patients younger than 40 years of age with a palpable breast abnormality, either US, diagnostic mammography, or Digital Breast Tomosynthesis (DBT) can be used for the initial evaluation. In this group of patients, the use of US as the primary imaging modality is reasonable[22] due to its greater sensitivity compared to mammography. However, if a suspicious mass is identified, bilateral mammography is recommended.[23]

Mammographic findings

In many studies, it has been found that architectural distortion (Fig. 2) is the most common abnormality of LGASC while asymmetry or high density masses have been reported less frequently. Microcalcifications are uncommon.[4,5,13,14] The architectural distortion may even be occult to conventional 2D imaging, whilst it is more often detected at tomosynthesis.

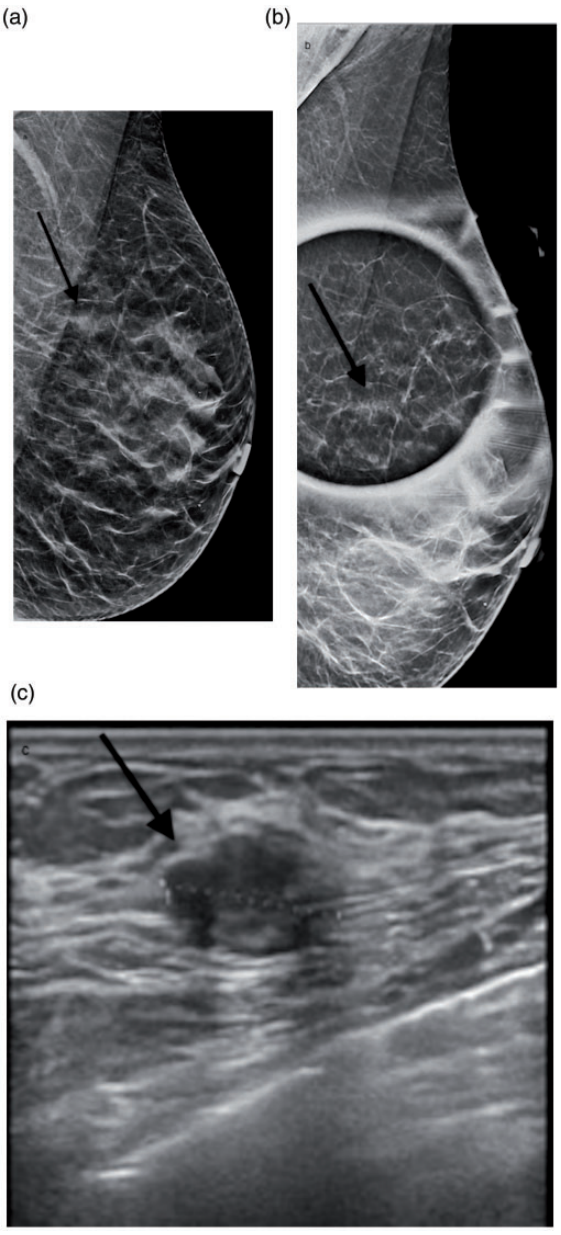

Figure 1. (a) DBT slice shows a focal asymmetry in the left upper-outer quadrant of a 54-year-old patient. (b) A subsequent additional targeted view is performed to study better the radiological features, confirming the focal asymmetry with fine linear microcalcifications. (c) On the following US, there is a hypoechoic mass with microlobulated margins of about 1.7 cm.

Rarely, there might not be mammographic clues of LGASC,[21] especially in heterogeneously or extremely dense breasts, in such cases, US is essential (Fig. 3).

Ultrasound findings

On US, LGASC may show as a hypoechoic mass with microlobulated or indistinct margins,[3,13] sometimes with internal vascularity at Doppler flow imaging[16]; Tan et al. reported a mass on sonography in all eight patients of their study. As to the US mass measurements, these ranged from 0.8 to 6 cm (mean 2.8 cm).[16]

Preoperative diagnosis of LGASC is rare, due to inherent limitations of analysis on fine needle aspiration (FNA) and core needle biopsy.[21]

Magnetic resonance imaging findings

Dynamic contrast-enhanced magnetic resonance imaging (MRI) of the breast might not add information and will not probably be helpful to differentiate between LGASC and other lesions. Very few published studies reported the MRI appearance of LGASC. It has been found that a mass with spiculated margins, heterogeneous enhancement, and early washout is the most common abnormality of LGASC.[3,24,25] Further studies are needed to assess the diffusion-weighted imaging features of LGASC.

Imaging differential diagnosis

The differential diagnosis between the LGASC and other breast diseases is only possible histologically, because there are no specific findings on mammography and sonography as LGASC shares features with both benign and malignant neoplasms: pathological examination is thus essential for the diagnosis.[17]

Diagnostic challenges

FNA cytology

FNA has a high sensitivity and specificity (close to 100%) for the diagnosis of metaplastic carcinomas (which are high-grade tumors).[26] The diagnosis of metaplastic carcinomas is based on the presence of conventional-type carcinomatous elements associated with unusual cellular or stromal components (especially metaplastic cells), keratin debris, and triple negativity: these histologic features are greatly helpful in accurate tumor typing.[26] FNA may be less accurate in the diagnosis of malignancy of LGASC, particularly because of the absence or subtlety of overt malignant characteristics, and this can result in misdiagnosis.[26,27]

The cellular yield varies depending on the technique employed and, thus, cellularity cannot be used as a reliable surrogate for malignancy. Histological examination reveals angulated sheets and tubular structures; epithelial cells are relatively monomorphic, which should alert the cytopathologist to be careful of their nuclear details, since the modest nuclear enlargement and irregularity can be difficult to distinguish. Sometimes, whorl-like arrangements of epithelial cells may hint at squamous differentiation, although

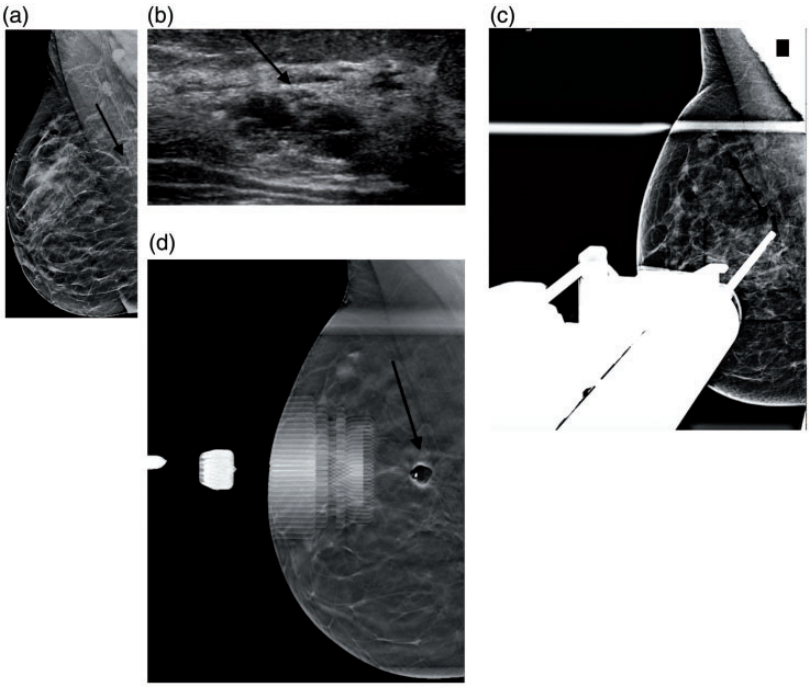

Figure 2. (a) 2D projections mammography shows – only in mediolateral oblique projection – an architectural distortion with a diameter of about 12 mm in the right upper-inner quadrant of a 46-year-old woman. (b) On US, there is a hypoechoic mass with indistinct margins, of uncertain nature. ((c) and (d)) We proceed to DBT vacuum-assisted breast biopsy which allowed us to diagnose LGASC.

unequivocal keratinisation is seldom seen. In some cases, a suggestion of myoepithelial cuffing may be perceived, reflecting the variable circumferential myoepithelial staining pattern observed by Kawaguchi and Shin.[28] Rarely, dispersed tumor cells with marked atypia and a rim of cytoplasm may be discerned, increasing the probability of malignancy. The background may be dirty with scattered mildly atypical naked nuclei and spindle cells, representing the stromal component. Thus, LGASC is considered to be a biphasic tumor, as it shows a dysplastic epithelium and spindle elements in the stromal tissue and this is reported as distinctive and diagnostic by Ferrara et al. and diagnostic by Sironi et al.[27]

Percutaneous image-guided biopsy

Despite the high sensitivity rates of image-guided percutaneous core-needle biopsy, such technique has the disadvantage of not allowing differentiation between invasive and noninvasive cancers, and lacks of sufficient tissue to define cancer biomarkers.[19] All the histological characteristics of LGASC may not be readily appreciated on a core needle biopsy specimen, being limited in nature and possibly fragmented.[12] US plays a key role in biopsy guidance, in fact US-guidance is currently considered the most cost-effective way to perform breast biopsy procedures.[29,30] Biopsies require a high degree of expertise and experience in order to choose the most appropriate imaging modalities for guidance (Stereotaxis, US, MRI).[31]

Stereotactic vacuum-assisted breast biopsy/ DBT-guided vacuum-assisted biopsy

Currently, vacuum-assisted breast biopsy (VABB) is first choice technique for breast tissue sampling because it removes a larger amount of tissue needed for reliable histopathological assessment compared to the spring-loaded devices, hence reducing the histologic upgrade rate. DBT-guided biopsy has been proven more accurate for lesion location than stereotactic VABB.[32,33] In fact, in DBT-vacuum-assisted biopsy, the target lesion is identified by choosing the DBT section with the best visualization of the lesion (Fig. 2).

Ultrasound-guided VABB

Generally, when a suspicious lesion needs to undergo biopsy and it is visible on US, US-guided biopsy may be chosen.[34,35] A stereotactic breast biopsy may be performed when a mammogram shows suspicious calcifications; however, if the calcifications are associated with a mass, US-guided biopsy may be performed (Fig. 4).

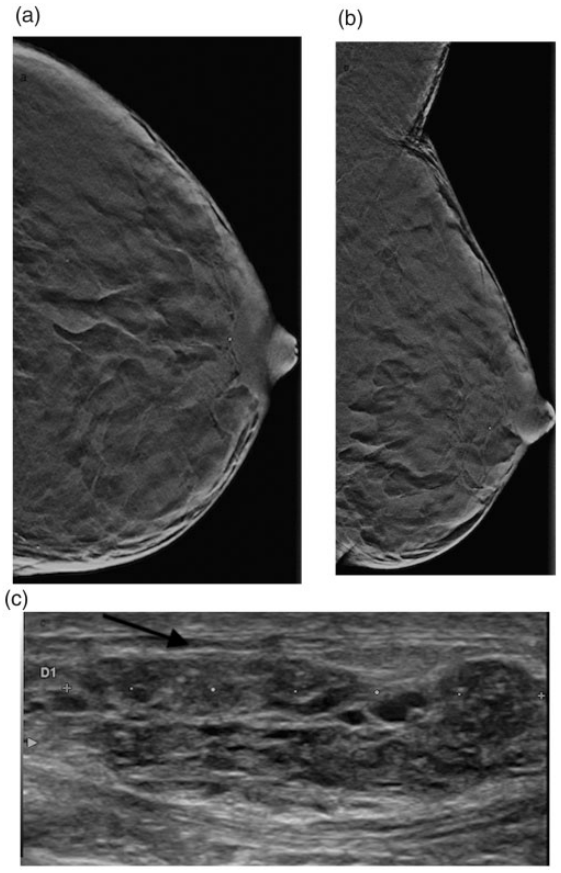

Figure 3. ((a) and (b)) Mammograms of a young woman with extremely dense breasts. There are no mammographic findings either in craniocaudal or mediolateral oblique projections. (c) On the other hand, on US, a suspicious mass appears in the left lower peri-areolar area.

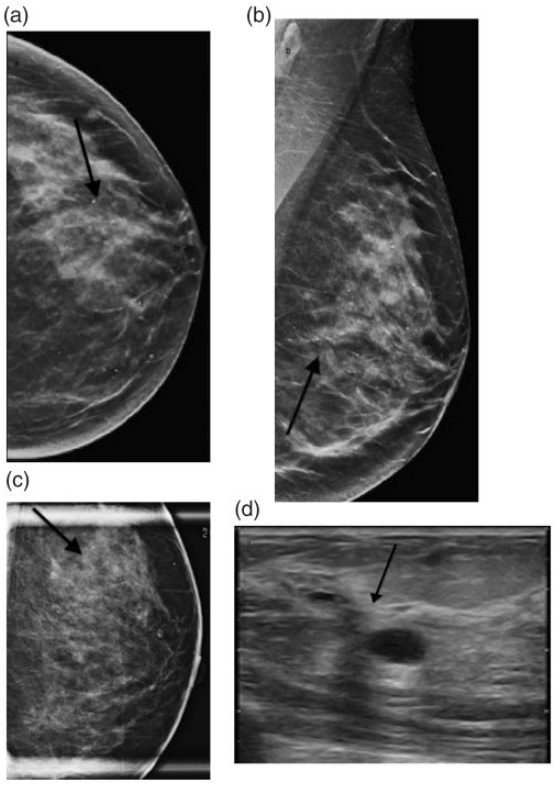

Figure 4. ((a) to (c)) In craniocaudal and mediolateral oblique projections of a 70-year-old woman, suspicious microcalcifications (black arrow) in the left external periareolar area are identified. (d) This finding corresponds in US scans, obtained with high-frequency probe, to a suspicious mass not circumscribed complex cystic/solid hypoechoic with microcalcifications associated.

MRI-guided VABB

Particularly in cases of MRI-detected lesions, the identification of a US correlate makes the biopsy procedure much easier; three-dimensional MRI reconstructions facilitate the location of LGASC lesions, so that they can be identified with targeted US, and US-guided biopsy can be performed with a minimal patient discomfort. If the lesion is only seen on MRI, then MRI-guided biopsy is performed.[31]

Surgical biopsy

In conclusion, diagnosis of LGASC on FNA and core needle biopsy can be difficult to achieve[14,16]; therefore, the excisional biopsy should be considered in order to reach a more definite histological diagnosis since the amount of tissue obtained is higher. However, surgical biopsy is associated with the difficulty of evaluating accurately the size and extent of the lesion, especially margin clearance and, in a locally aggressive lesion such as LGASC, subsequent management understandably depends on whether the excision margins are clear or not.[28] Often, the lesion presents peripheral clusters of lymphocytes, sometimes in a "cannon ball" pattern and this can help delineate the general boundaries and extent of the lesion.[12,36]

Macroscopy and histopathology

The typical gross appearance of LGASC is an ill-defined tumor with irregular borders, firm consistency, and a white/yellow cut surface.[9] On histology, LGASC shows a glandular and squamous differentiation in a stellate/infiltrating configuration, particularly, a well-developed glandular and tubular formation admixed with solid nests of squamous cells in a spindle-cell background. The carcinomatous component is characterized by small glandular structures and solid cords of epithelial cells.[11] All tumors show triple-negative phenotype, defined by the lack of expression of estrogen receptor (ER), progesterone receptor (PR), and HER2, with the lack of androgen receptor expression. The proliferation indices assessed according to

Ki67 ranged between 2 and 20% (mean, 11%; median, 10%).

Differential diagnosis

The differential diagnosis between the LGASC and other breast diseases is possible only histologically. A variety of lesions, including benign fibrosclerosing lesions with squamous metaplasia (complex sclerosing adenosis, radial scar, myoid hamartoma, pleomorphic adenoma (PA) without osseous or chondroid differentiation), tubular carcinoma, and syringomatous adenoma of the nipple (SAN) can be mistaken for LGASC.[37,38]

The differential diagnosis of LGASC from fibrosclerosing lesions is based on the absence of lobular configuration and on the infiltrative pattern of growth in LGASC. Histologically, LGASC differs from tubular carcinoma in the presence of squamous differentiation and triple negative phenotype.[39] Historically, LGASC and SAN have been described as separate entities, but an accurate distinction is difficult as seen in the primary excision. Reports in the literature have mislabeled these lesions[39] and the terms "LGASC" and "infiltrating syringomatous adenoma" have been used, by some authors, interchangeably.[19] More recently, it has been suggested that LGASC and SAN are the same lesion of supposed metaplastic origin, although arising in different anatomical locations: LGASC within the breast parenchyma, SAN is limited to the epidermal layer of the skin/nipple. Both LGASC and SAN are CK5/6 and p63 positive,[26] and ER, PR, and HER2 negative;[12,21] both lesions present a locally aggressive behavior with a potential for local recurrence. Furthermore, it is also important to distinguish LGASC from benign fibrosclerosing lesions with squamous metaplasia; in particular, radial scar/complex sclerosing lesion represents a benign lesion which can be misdiagnosed as a malignant tumor due to the attenuating myoepithelial cell layer. Usually, LGASC stains inconsistently for various myoepithelial markers and cytokeratins;[40] instead, in radial scar/complex sclerosing lesion, myoepithelial cell markers are present without the inconsistent pattern of expression seen in LGASC.[26] The differential diagnosis between myoid hamartoma and LGASC is based on the presence of varying amounts of smooth muscle cells[12] in myoid hamartoma; conversely, LGASC does not contain smooth muscle cells. Squamous metaplasia can also be detected in breast PA[26] and, if the osseous or chondroid differentiation is missing, the distinction between LGASC and PA is not simple. Although PA consists of epithelium and myoepithelial, myoepithelial staining patterns mentioned above are not likely to be seen in PA. Although PA is composed of epithelial and myoepithelial cells.

Management of LGASC

LGASC presents a risk of local recurrence after incomplete excision even in low-grade cases.[19] In several studies, local recurrence was demonstrated in women treated with local excision only, for example, 8 out of 11 in a 1987 study by Rosen and Ernsberger and 5 out of 19 in a 1993 study by Van Hoeven et al. Conversely, in a study by Tan et al. that retrospectively evaluated eight patients with LGASC, five of whom were treated with wide excision and three of whom underwent total mastectomy, there was no recurrence in any of the patients during a median follow-up time of 41.1 months.[16]

Other authors argue that, due to the indolent natural history of LGASC, local excision with margins of 1 cm is sufficient, provided that lymph nodes are clinically unremarkable. However, aggressive treatment with wide breast excision (a procedure which removes the cancer and the immediate area of surrounding breast tissue) is recommended due to the relatively frequent risk of local recurrence presumably because of incomplete or marginal excision.[19,21]

In the literature, there are very few documented cases of development of distant metastases from adenosquamous carcinoma, and in large lesions only (>30 mm in diameter), after multiple local recurrences, or after transformation into high-grade tumor. The precise and careful assessment of surgical resection margin status is mandatory. After an adequate local excision, no clear benefit was found for adjuvant therapies such as chemotherapy and radiotherapy.[14,40,41]

Adjuvant radiotherapy and chemotherapy should probably be associated with improved survival only for tumors larger than 3 cm, in cases of proven lymphovascular invasion, or with lymph node metastasis on histopathology. Only one case of local breast skin recurrence was reported in the literature: it was mainly composed of a keloid-type mesenchymal component, and was observed after conservative surgical approach to an adenosquamous carcinoma of the breast with sarcomatous stromal overgrowth (SO).[42] The tumor was associated with the rapid development of brain and skull metastases. The local recurrence lacked any squamous component and only presented a few benign-looking glandular structures, initially misinterpreted as a benign skin lesion.[1] This very particular case shows that some of these types of lesions may harbor in both primary tumor and recurrence a massive SO of keloid-like component, and can be misdiagnosed as benign lesions. Careful clinicopathological correlation and multidisciplinary tumor

board assessment are invaluable to reach an accurate diagnosis of recurrences.

Conclusion

Low-grade adenosquamous carcinoma of the breast is a rare form of "metaplastic breast cancers", representing $< 1\%$ of all breast carcinomas. Contrary to the aggressive nature, triple-negative, chemo-resistant features of most metaplastic breast cancers, LGASC is described as an indolent tumor, with a low metastatic potential and it also tends to have a better overall prognosis.

Author's contribution

Conceptualization of the work, original draft preparation, final approvement, agreement to be accountable: Giovanna Romanucci and Francesca Fornasa; analysis of data, original draft preparation, final approvement, agreement to be accountable: Andrea Quaglia; interpretation of data, original draft preparation, final approvement, agreement to be accountable: Sara Mercogliano and Elisabetta Carucci; acquisition of data, original draft preparation, final approvement, agreement to be accountable: Maria Lunardi, Andrea Caneva and Chiara Benassuti.

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