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Bilateral synchronous low-grade adenosquamous carcinoma of the breast: A Case report with review of the current literature

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ABSTRACT

INTRODUCTION: Low-grade adenosquamous carcinoma (LGASC) is a rare, unique variant of metaplastic breast carcinoma, characterized by clinical indolence and low-grade cytomorphology. Being clinically asymptomatic with indefinite imaging characteristics, diagnosis is solely dependent on histopathology.

PRESENTATION OF CASE: A 68-year-old woman presented to the Breast Health Center with mammogram-detected left-sided retroareolar calcifications. She had a three-year history of non-progressive bilateral nipple inversion, and was otherwise asymptomatic. Left breast biopsy revealed atypical metaplastic squamous epithelial cells. Subsequently a wire-guided lumpectomy diagnosed a syringomatous adenoma of the nipple. A surveillance MRI identified a contralateral breast lesion, which on core biopsy showed an atypical adenosquamous lesion. Bilateral central mastectomies with bilateral sentinel node biopsies were undertaken.

Histopathological review of both breast specimens confirmed the unique features of adenosquamous carcinoma identified by an infiltrative pattern of small rounded compressed angulated glands with squamous differentiation and low-grade cytomorphology. The tumors were triple negative [ER, PR, HER2]. The sentinel lymph nodes were negative.

CONCLUSION: Bilateral synchronous LGASC of the breasts is exceedingly uncommon and remains a diagnostic and therapeutic challenge. Despite being triple negative, due to its indolent behavior, recognition of this unusual primary breast malignancy is important as it has a more favorable prognosis. Yet, due to its rarity, there are no guidelines for best practice management regarding the role of adjuvant therapy.

1. Introduction

Low-grade adenosquamous carcinoma (LGASC) of the breast is exceedingly uncommon, belonging to the family of 'metaplastic breast cancers' which represent <1% of all breast carcinomas [1]. In contrast to the highly aggressive, triple-negative, chemo-resistant features of most metaplastic breast cancers, LGASC portends an indolent course, with a low metastatic potential and thus an improved prognosis [2,3]. Reports of LGASC in the published literature are limited. We herein describe a case of bilateral synchronous LGASC, an extremely rare occurrence.

2. Case report

A 68-year-old female was referred with suspicious clusters of 2.5 × 5.5 cm calcifications in the retroareolar left breast on mammogram (Fig. 1) and an unremarkable ultrasound. On risk factor stratification, menses began at age 10, and at age 45 she underwent a hysterectomy and unilateral oophorectomy for benign disease that required hormone replacement therapy for three years. She was nulliparous with no significant family history of breast/ovarian cancer. Physical exam was non-contributory, with no evidence of nipple discharge, skin changes, or palpable breast masses or axillary lymphadenopathy. Breasts were symmetrical with a long-standing history of bilateral nipple inversion.

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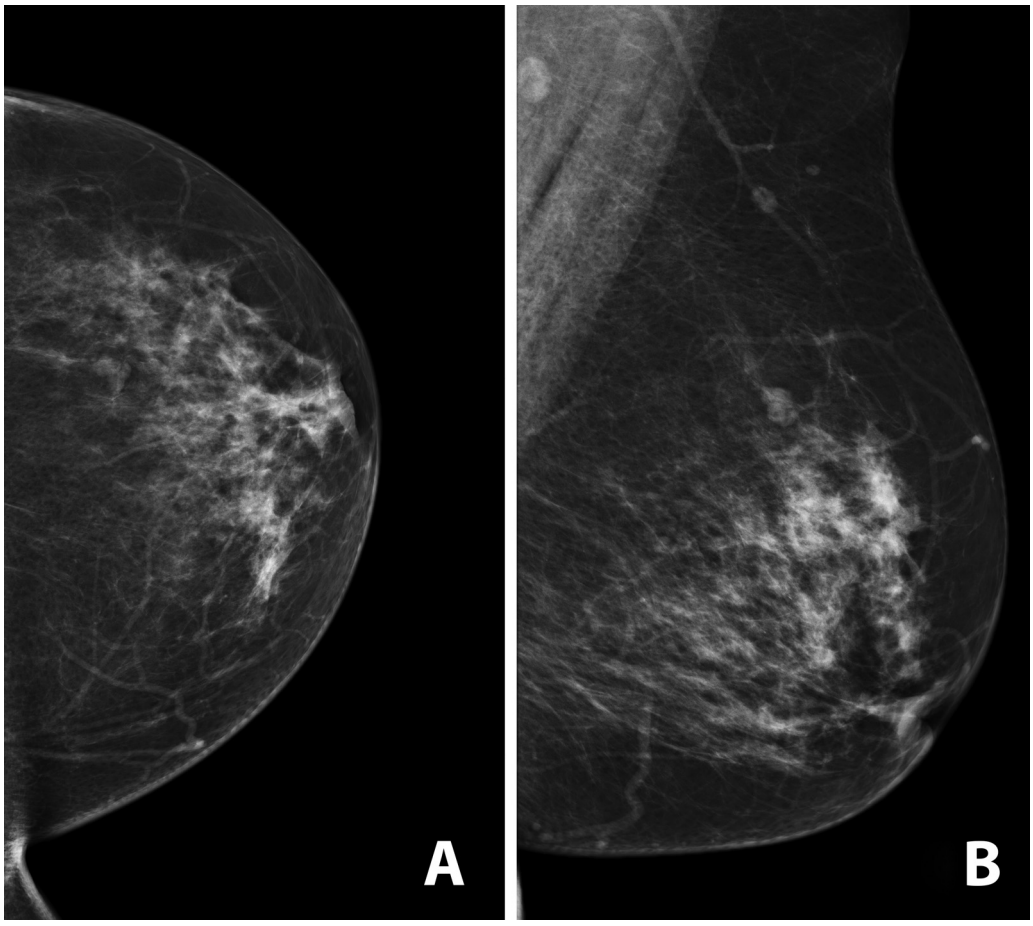

Fig. 1. Mammogram of the left breast shows irregular spiculated calcifications in a retroareolar distribution on both compressed views.

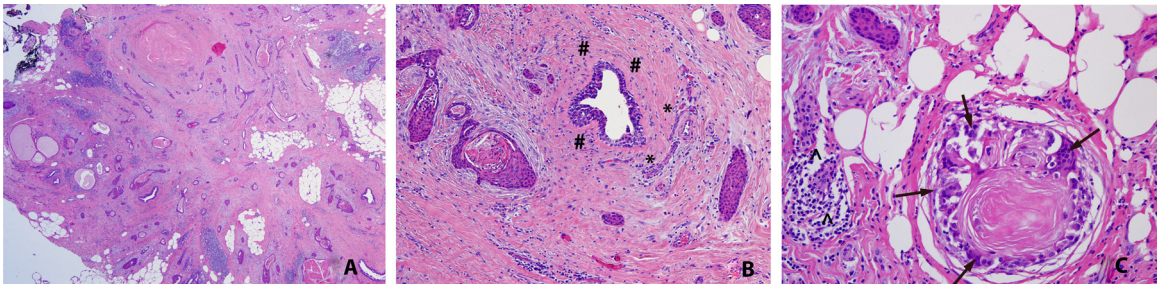

Fig. 2. Excision biopsy of left breast lesion. Photomicrograph of haematoxylin and eosin stained slide at low (A), medium (B) and high (C) magnifications show a focal nodular lesion (A) with compressed duct-like structures (*) surrounded by fibrotic stromal cells (#) (B) admixed with proliferating atypical squamous metaplastic cells (→) and lymphocytic infiltration (^) (C).

Stereotactic biopsy of the left breast identified irregular groups of metaplastic atypical squamous epithelial cells with granulomatous inflammation and calcifications raising the suspicion of microinvasive carcinoma. With the possibility of cancer, the patient elected to undergo a wire-guided lumpectomy. Histopathology identified mildly proliferative fibrocystic changes with duct hyperplasia, sclerosing adenosis, apocrine metaplasia, fibroadenomatoid nodules and multiple intraductal papillomas with a focal nodular lesion composed of proliferating squamous metaplastic cells with compressed duct-like structures surrounded by fibrotic stromal cells [Fig. 2A–C], diagnosed as syringomatous adenoma of the nipple with no evidence of invasive/in-situ carcinoma.

Due to the discordant biopsy and lumpectomy pathology, and in keeping with patient preference, wide excision of the left breast was planned, which was temporarily postponed due to comorbid pulmonary disease. A follow-up MRI nine months post-operatively discovered an incidental spiculated nodule in the retroareolar right breast. An ultrasound-guided right breast core biopsy identified an atypical adenosquamous lesion suspicious for low-grade carcinoma. She was medically optimized and underwent bilateral central mastectomies with sentinel lymph node biopsies.

Histopathology confirmed low-grade adenosquamous carcinoma of the right breast with atypical infiltrating metaplastic squamous cells surrounded by stromal lamellar fibrosis and lymphocytic aggregates in the background of a complex sclerosing lesion (Figure 3A–C). The residual left breast tissue showed similar features supporting the presence of bilateral LGASC (Fig. 4A–C). Tumour cells were negative for ER, PR, and Her2, and the lymph nodes were negative for metastatic disease.

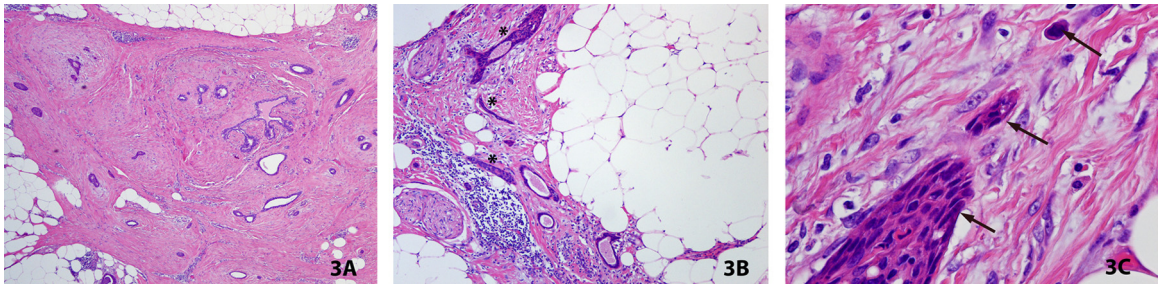

Fig. 3. Right breast central mastectomy. Photomicrograph of haematoxylin and eosin stained slide at low (A), medium (B) and high (C) magnifications show a complex sclerosing lesion (A) with infiltrating duct-like structures (*) (B) and single infiltrating atypical squamous cells with metaplastic squamous cells lining the ducts (→) (C).

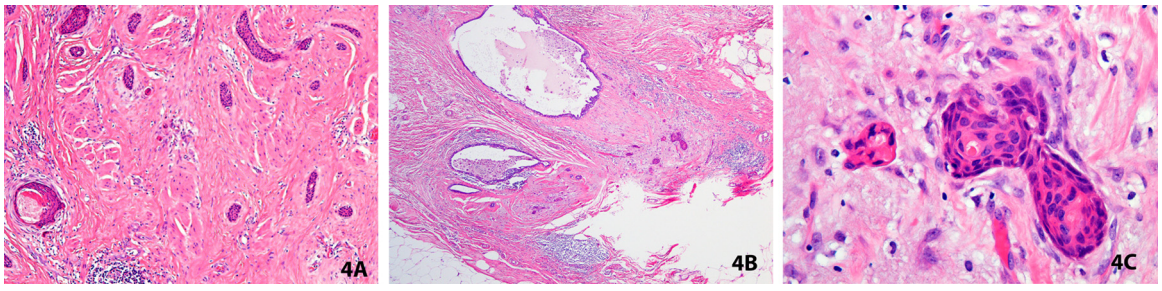

Fig. 4. Left breast central mastectomy. Photomicrograph of haematoxylin and eosin stained slide at low (A), medium (B) and high (C) magnifications show similar features of infiltrating atypical squamous cells in the background of dense stromal lamellar fibrosis and lymphocytic aggregates.

Postoperatively, radiation and medical oncologists decided there were no evidence-based guidelines for adjuvant chemoradiation and she is well at 4 years follow-up.

3. Literature review

A review of the published literature using PubMed and Medline identified all reports of LGASC of the breast. Case reports and series were analyzed for the following data: patient age, laterality of lesion, clinical presentation, diagnostic imaging techniques, histopathology, treatment and outcomes. Case reports/series that describe sporadic cases of LGASC without providing clinical data were excluded.

A total of 18 manuscripts (1987 to present) describing 109 cases of LGASC are summarized in Table 1 [1–18]. Patients' ages range from 19 to 88, with two cases of bilateral LGASC being reported. Majority of patients (89%) presented with a palpable breast mass (97/109). Almost all patients underwent mammogram and ultrasound as their initial radiologic work-up, with calcifications and/or a hypoechoic mass being most commonly described. Patients underwent surgical excision (78/109) or a mastectomy (31/109). Though early studies by Rosen(36%) and Van Hoeven(20%) reported relatively frequent rates of recurrence (4/11 and 5/25), most patients reported in the recent literature had no subsequent disease progression.

4. Discussion

LGASC of the breast was described by Rosen and Ernsberger in 1987 [18] and has since been reported sporadically in the literature. Currently the WHO classifies LGASC under "metaplastic carcinoma", a group of tumours defined by neoplastic epithelium that differentiates into squamous cells and/or mesenchymal-appearing elements. Clinically, LGASC occur in patients of any age (19-88) and commonly present as a palpable mass rather than an incidental finding on mammography [12,17,19]. Though LGASC is locally invasive, and despite a 'triple-negative' profile, metastases are rare and patients have an overall good prognosis, different from other metaplastic carcinomas of the breast [1,3,6,7,17,18].

LGASC is nonspecific on mammographic and sonographic imaging, mimicking both benign and malignant neoplasms. Commonly a spiculated lesion on mammogram and an irregular hypoechoic mass on ultrasonography are identified. LGASC radiology is limited to case-reports and case-series with no pathognomonic findings; features include a nodular or stellate appearance on mammogram and a solid irregular hypoechoic mass with poorly-defined borders on ultrasound [7].

Accurate diagnosis of LGASC preoperatively is often impossible at fine-needle aspiration cytology (FNAC) due to a paucity of classical cytological features of malignancy [5,11,14–16]. At core biopsy the overall architecture is not appreciable, and intraoperative frozen section is limited due to sampling [13,19]; therefore, preoperative confirmation is rare, as seen in the biopsy from the left breast in our case. Nuclear uniformity/enlargement, monomorphism, keratin debris, and the presence of metaplastic squamous cells may reduce false negative rates on FNAC [5,13]. Immunomarkers such as p63 may aid in recognizing the squamous elements that facilitate exact tumor typing; however, this requires a high preoperative index of suspicion [12].

Due to the risk of local recurrence, aggressive treatment with wide breast excision or mastectomy is recommended as microscopic peripheral extensions of this tumor within the normal parenchyma affects the evaluation of the post-resection margins [19]. Other authors argue that due to the indolent natural history of these tumors with low metastatic potential, local excision with margins of 1 cm is sufficient, provided lymph nodes are clinically unremarkable [3].

It is not uncommon for LGASC of the breast to coexist with additional breast pathologies. Several authors report associations with sclerosing lesions [3,12], fibroadenoma (FA), phyllodes tumors, carcinoma in-situ, fibroepithelial lesions [3], and adenomyoepithelioma [20]. LGASC commonly occurs in the background of radial scars (RSL)/complex sclerosing lesions(CSL), as seen in our case. Among 20 RSLs reported by Wilsher, 60% contained adenosquamous proliferation/papilloma, indistinguishable from

Table 1
Literature review "low-grade adenosquamous carcinoma of the breast"—PubMed & Medline 1987 to present. Exclusion criteria—refer to manuscript.

Reference	#cases	Age (y)	Later-ality	Presentation	Imaging	Biopsy findings	Treatment	Coexisting lesions	Node biopsy	Outcome
Tan [3]	8	29–49	NS	Palpable mass (8)	MG (5) U/S (8)	CBx (7): Phyllodes (3), LGASC (3), fibrocystic changes EXBx: IDC + ACC + LGAC	SgEX (4) Mx (4)	FA, ACC, IDC, RSL, CSL, phyllodes	SLNB (5)	NS
Cha [4]	1	69	Rt	Palpable mass	MG – microcalcifications	CBx—'fibroadenoma with squamous metaplasia'	Mammotome excision	None	NS	NS
Bataillon [5]	3	54	Lt	Palpable mass	MG	FNA—malignancy Frozen section—FEL	SgEX		SLNB	3 years post-op ILC BRCA-2
		56	Lt	MG detected	MG, U/S-guided FNA	FNA—tubular carcinoma CNBx—FC	Lumpectomy	ILC (contralateral)	SLNB	6 years disease-free
		81	Rt	Palpable mass	MG	FNA—AC with squamous metaplasia	Lumpectomy Chemo	IDC, +ve nodes (contralateral)	ALND	6 years disease-free survival
Wilsher [6]	1	45	B/L	Palpable mass (Rt)	U/S, MG	FNA: FA CBx—CSL	Nipple-sparing Mx	CSL, FA	SLNB	Incidental finding LGASC left breast in six radial scars
Scali [7]	10	30–81	NS	Palpable mass (5) MG finding (3) Nipple changes (2)	MG (10) U/S (10)	Scattered glandular and squamous components	Mx (3), BCT (7), Radiation (7), Chemo	NS	NS	Follow-up 2–11.5 years No metastases 1 local recurrence
Alipour [8]	1	33	Lt	Inflammation & abscess	MG, U/S, CT chest, abdo, pelvis	Abscess wall —IDC	BCT, chemo, radiation	Abscess	ALND	4 years no recurrence
Chuthapisith [9]	1	55	Lt	Palpable mass	MG: calcified mass U/S	EBx—LGASC with osseous metaplasia	SgEX	Sclerosing FA	NS	Repeated recurrences: 4 years, 1 year, 4 months
Kawaguchi [10]	30	20–85	Rt (15) Lt (15)	Palpable mass (29)	NS	CBx (14) EXBx (12)	EXBx (29) Mx	DCIS, SL (6), Papilloma	SLNB (2)	NS
Bigotti [2]	1	65	Rt	Palpable mass	U/S, MG	FNAC CBx—IDC	Chemo Mx	None	ALND	Disease-free at 17 months post-op
Sironi [11]	1	74	Lt	MG spiculated nodule	U/S-guided FNAC	FNA—malignant epithelial cells	SgEX	None	NS	NS
Agrawal [12]	1	19	Lt	Palpable mass	U/S: hypoechoic mass	CBx atypical adenosquamous EBx—adenosquamous lesion	Mx	RSL	None	No disease recurrence
Noel [1]	1	62	Rt	U/S hypoechoic mass	U/S MRI—5 mm nodule	CBx: LGASC	SgEX	None	NS	BRCA-1 +ve
Ho [13]	4	51–62	Lt (3) Rt	MG detected (2) Palpable mass (2)	U/S-guided FNAC U/S (2) MG (2)	FNAC—atypical cells CBx (2)—DCIS, atypical SL Frozen section	SgEX, Mx (2), EXBx, Chemo	IDC DCIS CSL	ALND (3)	No disease recurrence
Ferrara [14]	1	57	Lt	Painless mass	NS	FNAC—malignancy Frozen section—cancer	BCT Radiotherapy	Spindled stellate cells	ALND	Disease-free 3y postop
Shizawa [15]	1	47	Lt	Palpable mass	MG & U/S—no cancer	FNAC—atypical squamous cells EXBx	Mx	None	ALND	Well 16 months
Krigman (1996) [16]	1	57	Rt	Palpable mass	MG: nodular mass	FNA—rare atypical cells	EXBx	Papillomatosis SA	NS	NS
Van Hoeven [17]	32	33–88	Rt (17) Lt (14) B/L (1)	Palpable mass (32)	NS	NS	EXBx (19) Mx (13)	FC, Papilloma (12), AME (3), CS (3)	ALND (12)	12–124 months follow-up 5/25 recurrences
Rosen (1987) [18]	11	42-76	Rt (6) Lt (3)	Palpable mass (11)	NS	EXBx (7)	Mx (4) EXBx (7)	Osteocartilagin-ous metaplasia	ALND (4)	4 recurrences (1–3.5 years)

ACC: adenoid cystic carcinoma; ALND: axillary lymph node dissection; AME: adenomyoepithelioma; BCT: breast conserving therapy; CBx: core biopsy; CS: collagenous spherulosis; EXBx: excisional biopsy; FC: Fibrocystic change; FEL: fibroepithelial lesion; FNAC: fine needle aspiration cytology; Lt: left; MG: mammogram; Mx: mastectomy; NS: not specified; Rt: right; SA: sclerosing adenosis; SgEX: surgical excision; SLNB: sentinel lymph node biopsy; U/S: ultrasound

LGASC, suggesting adenosquamous proliferation of RSL may be a benign precursor to LGASC [21].

On gross examination, LGASCs have irregular borders, firm consistency, and a white/yellow cut surface [19]. On histology, LGASC shows glandular and squamous differentiation in a stellate/infiltrating configuration. Small tubular glands in collagenized stroma with low-grade cytologic atypia and rare mitoses/necrosis may be seen; however, precise identification is challenging [7]. Thus, accurate recognition of LGASC from 'mimickers' is difficult; such lesions include benign fibrosclerosing lesions (sclerosing adenosis, radial scar), tubular carcinoma, and syringomatous adenoma of the nipple (SAN). Differentiation of LGASC from fibrosclerosing lesions is supported by the absence of lobular configuration in LGASC. Histologically, LGASC differs from tubular carcinoma by the presence of squamous differentiation [19].

Traditionally, LGASC and SAN have been regarded as separate entities; accurate distinction remains a considerable challenge as seen in the primary excision sample of the left breast in our case. Reports in the literature have mislabeled these lesions [5,19], with some authors currently using the terms 'LGASC' and 'infiltrating syringomatous adenoma' synonymously [1,13,14]. Both lesions are locally aggressive with a propensity for local recurrence. An emerging school of thought proposes that LGASC and SAN are the same lesion of putative metaplastic origin, though arising in different anatomical locations. SAN is proposed to arise from the pluripotent adnexal epidermal keratinocytes with dual follicular and sweat gland differentiation, while LGASC is from the myoepithelium [14,22]. Thus, while LGASC is located within the breast parenchyma, SAN is limited to the epidermal layer of the skin/nipple. On microscopy, LGASC and SAN are deemed "essentially identical" [19]; both are composed of well-differentiated infiltrative glands with an angulated/polliwog appearance. Differentiation between LGASC and SAN may therefore be impossible, particularly if the former involves the nipple areolar complex as seen in our case (Figs. 2 & 4). Both LGASC and SAN are positive for CK5/6 and p63 [10], and negative for ER, PR, and HER2 [5,21]. Boecker et al. showed LGASC and SAN contain p63+/K5/K14+ tumor cells, K10+ squamous, and K8/18+ glandular cells. They concluded that these two lesions are identical with p63+/K5/14+ cells playing a role in neoplastic transformation of both entities [22].

This index case is the third bilateral LGASC reported. Van Hoeven described LGASC of the left breast with subsequent development 1 year later in the right breast [17]. Additional clinical details are unavailable. Wilsher and Snook described a right-sided LGASC with a second focus of LGASC within six radial scars in the left breast 1 month later [6]. Such bilateral cases raise the possibility of LGASC being a complex multicentric disease and therefore perhaps mastectomy should be recommended as the standard practice of care rather than wide local excision that can cause increased recurrences as seen in the case-series of Rosen (36%) [18] and Van Hoeven (20%) [17].

5. Conclusions

Given the rarity of LGASC of the breast, a large number of 'unknowns' that continue to pose clinical challenges include: the precise etiology/histopathogenesis and the lack of pathognomonic diagnostic radiological and cyto-histo-pathological features. The precise relationship between LGASC and SAN remains disputed with speculation of whether they represent a continuing spectrum or are two independent progressive proliferative breast lesions. Increased clinical recognition of this unusual primary triple-negative breast cancer is imperative due to its clinical indolence and slow evolution with excellent survival.

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