Significance of adenosquamous proliferation in breast lesions

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ABSTRACT

Adenosquamous proliferation (ASP), characterised by ductal structures with a dual glandular and squamous phenotype within desmoplastic stroma, is essentially a hallmark of various sclerosing lesions of the breast (SL) and breast lesions with sclerosis (BLWS), not including sclerosing adenosis. In radial scar/complex sclerosing lesion (RS/CSL), clonality has been previously demonstrated in microdissected ASP. SL/BLWS encompass a diverse range of pathological entities that historically have an equally diverse list of names, often for histologically alike or identical lesions at different anatomical locations. In common they are comprised of one or more components of fibrocystic or proliferative breast disease and papillomata, which become distorted and even obliterated by a sclerosing process that appears to be associated with and/or secondary to ASP, which in an individual lesion may be inconspicuous at the time of biopsy. The histological overlap of various SL/BLWS with RS/CSL, in which a nidus containing ASP is pathognomonic of early lesions, also supports a common element of ASP across various SL/BLWS. SL/BLWS show an interesting association with low-grade metaplastic carcinoma, particularly low-grade adenosquamous carcinoma (LGASC) with which, they appear to form a histological and possible biological spectrum because ASP and LGASC share similar histological and immunophenotypical characteristics. The presentation of ASP in various SL/BLWS will be discussed.

INTRODUCTION

Adenosquamous proliferation (ASP) of the breast¹ is a lesion characterised by compact ducts with both glandular and squamous features within a variable spindle cell stroma. They are most commonly encountered in the context of various sclerosing breast lesions (SL), or in subsets of benign entities that may show sclerosis (breast lesions with sclerosis (BLWS)), for example, intraduct papilloma (IP) and nipple adenoma (NA). Historically, various nomenclatures have been used for histologically alike, to essentially identical SL/BLWS at different anatomical locations. They all similarly occur at a broad age range. Histologically, they share in common variable degrees of proliferative, fibrocystic and papillomatous change and a variable content of ASP. SL/BLWS often show temporal variability, for example, in radial scar/complex sclerosing lesion (RS/CSL), an early and late phase is typical. They may mimic carcinoma—clinically, radiologically and histologically and indeed also show an association with epithelial atypia, in-situ and invasive mammary carcinoma. SL/BLWS show an interesting

association with low-grade metaplastic carcinoma, particularly low-grade adenosquamous carcinoma (LGASC) with which, they seem to form a histological and possible biological spectrum.¹ The distinction of a SL/BLWS, for example, RS/CSL with prominent ASP and LGASC can be challenging.^{1,2}

RS/CSL is probably the most common SL encountered by pathologists and one which historically has the most diverse list of names.^{3–17} Micropapillomata are not infrequently seen in RS/CSL, but when sclerosing changes occur in predominant papillomata they are termed ‘sclerosing papilloma (SP)’, which is related to the lesion termed ‘ductal adenoma (DA)’ introduced by Azzopardi and Salm.¹⁸ Infiltrating epitheliosis (IE), currently not a WHO recognised entity, is considered to lie within the spectrum of RS/CSL. It shows a predominance of florid usual ductal hyperplasia (UDH) and/or a UDH-like process. The ‘pattern’ may form a histological continuum with the newly WHO recognised entity, tall cell carcinoma with reversed polarity (TCCRP).^{19–21} NA (florid papillomatosis (FP) of the nipple)²²—the sclerosing papillomatous variant, and the deeper variant—subareolar sclerosing duct hyperplasia (SSDH),²³ may show histological features overlapping with RS/CSL, SP and DA. Syringomatous tumour (ST) resembles an LGASC confined to the nipple, the latter typically presenting within deeper and peripheral breast tissue, but of which, has also been diagnosed in a pure nipple location²⁴ and the two indeed may represent the same lesion.²⁵ They have a dual squamous and glandular phenotype and closely resemble the ASP seen in the context of SL/BLWS, but the latter is the predominant histological feature.

The aetiology of RL/CSL (and related SL) has been debated over time, but most recently it is considered that they may represent non-obligate clonal, neoplastic precursor lesions.^{26–28}

The nature of ASP and its appearance in various SL/BLWS will be discussed.

ADENOSQUAMOUS PROLIFERATION

ASP is an epithelial proliferation with a dual glandular and squamous phenotype, typically within a variable spindle cell (desmoplastic) stroma forming a lamellar cuff, and often with a syringoid appearance. ASP often appears to stream-out from or peel-off pre-existing ducts. It is not recognised as a specific entity by the WHO, yet it is essentially a hallmark of SL/BLWS, but may rarely be seen in other settings such as fibroepithelial lesions. The appearance is essentially histologically and immunophenotypically the same as the neoplastic

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proliferation characteristic of LGASC.¹ Indeed, using next generation sequencing (NGS) of microdissected ASP from RS/CSL, it has been shown to be a clonal proliferation in that context at least.²⁷ This may help explain the association of various SL/BLWS with LGASC and also the challenges in distinguishing such lesions with prominent ASP from an LGASC.^{1 27} LGASC is commonly reported in association with or emanating from benign proliferative and SL such as RL/CSL (including IE), IP, adenomyoepithelioma and NA.^{24 26 29–33}

In common with LGASC (and ST), ASP is triple negative for oestrogen and progesterone receptors and HER2, and displays coexpression of high-molecular weight cytokeratins such as cytokeratin 5/6 and p63. It lacks morphologically and phenotypically normal myoepithelial cells, showing their inconsistent presence, and is typically surrounded by reactive myofibroblasts, which express myoid immunomarkers but do not coexpress p63 as would myoepithelial cells. Therefore, immunohistochemistry cannot be used to distinguish a SL/BLWS rich in ASP and LGASC. Their distinction is typically based on the extent of ASP and degree of infiltration into surrounding breast tissue. ASP at least in the context of an RS/CSL appears to regress and disappear over time ('burns out'), being characteristic of early RS/CSL and diminished to absent in late RS/CSL where the nidus is replaced by fibroelastosis.¹ Suster *et al*³⁴ described four cases of 'syringomatous squamous tumours of the breast' ranging from 0.5 cm to 1.5 cm, which resembled LGASC, that they theorised may represent a preneoplastic or low-grade neoplastic process and a possible precursor stage of LGASC.

RS/CSL INCLUDING SO-CALLED IE

RS is perhaps the most recognisable term for this relatively frequently encountered SL. RS is a translation of 'strahlige narben' in German used by Hamperl³ in 1975 due to its stellate architecture. The term 'proliferation centre' (of Aschoff) is attributed to Ludwig Aschoff.⁷ However, 'proliferative growth centres' were described by Schaper and Cohen in a 1905 publication as a general embryological and pathological concept not specific to breast⁸ and Aschoff's textbook⁹ later referenced that publication. Numerous epithets exist (figure 1).^{3–17}

RS have a characteristic floral architecture, with ducts radiating from a central nidus out to a peripheral corona with a rosette-type appearance, whereas CSL may be more disorganised and sometimes nodular in appearance, and can be formed of merging adjacent smaller lesions.^{16 35} The nidus (centre) contains ASP at its inception, with fibroelastosis inversely proportional to the amount of ASP which reduce/involute over time.¹ It typically arises within an area of hyperplasia, fibrocystic change±micro-papillomata, which forms its corona. CSL shows a greater disturbance of architecture and may include papilloma formation, apocrine metaplasia and sclerosing adenosis.^{16 35} The ASP appears to essentially distort the latter and to consequently induce the stellate/distorted architecture.^{1 27} The overall incidence is 4.7%–8.2%.²⁶ The incidence on needle core biopsy (NCB) is 1%–2%.³⁶

A zone of stromal and periductal elastosis is seen as pathognomonic of an RS/CSL and is indeed a key component of the nidus in late lesions. However, this is a secondary, degenerative feature after an initial proliferative phase, along with fibrous sclerosis. Elastosis is not unique to an RS/CSL and its presence may lead to over diagnosis of the latter. Elastosis is seen in various benign breast diseases (eg, duct ectasia and fibrocystic disease) and is common in carcinoma.^{12 37} Parfrey and Doyle³⁸ found that in fibrocystic disease, stromal and periductal elastosis were related to the degree of epitheliosis (UDH).

Figure 1 Early radial scar/complex sclerosing lesion. (A) Adenosquamous proliferation (ASP) in area of fibrocystic change (H&E low-power overview). (B) Detail of ASP (H&E medium power). (C) Coexpression of CK5/6 and p63 by ASP (CK5 (red)/p63 (brown) dual staining—medium power). (D) Coexpression of CK5/6 and p63 by ASP (CK5 (red)/p63 (brown) dual staining—medium power). (E) Myosin heavy chain—muddy blurry staining of desmoplastic reaction. (F) ASP is oestrogen negative (between arrowheads).

In histological and electron microscopy studies of RSs, Anderson and Battersby^{39 40} suggested that RSs were progressive lesions that could be divided into early and late forms. The descriptions of RSs provided correlates with early (ASP-rich, fibro-elastosis poor) and late (ASP poor/absent, fibro-elastosis rich) RS/CSL.¹ Histologically, early RS/CSL are characterised by a nidus containing ASP set within loose mucoid stroma with invariably chronic inflammatory cells, with a peripheral corona comprising elements of fibrocystic disease, often with UDH. Small papillomata may occur. There may be an ill-defined nidus or multiple coalescing nides and a nidus may form a tumour-like focus mimicking a miniature LGASC; the distinction from the latter may be difficult, but the proliferation is typically regarded as benign if it remains confined to the nidus and does not permeate significantly beyond the corona and/or into adipose tissue. In time the ASP appear to involute and the nidus contains residual ducts with an often-incomplete myoepithelial or myoepithelial-like layer within fibroelastosis. Ductal scars may also be apparent. The end result (late RS/CSL) is an often stellate-shaped, 'washed out' fibroelastotic scar with the surrounding corona variably remaining.¹

RS/CSL can be associated with neoplasia, typically in-situ and/or invasive ductal or lobular carcinoma that may arise directly within the corona. Small RS (<0.5 cm) are unlikely to be associated with an adjacent carcinoma.⁴¹ RS/CSL rarely arise in the absence of proliferative breast disease (PBD) and the increased risk for carcinoma (up to twofold) is generally attributable to the category of coexistent PBD.⁴² The scar-like architecture is therefore almost incidental to the formation of common forms of neoplasia.⁴³ The risk of disease 'upgrade' at excision following a diagnosis of RS/CSL depends on the presence or absence of an associated high-risk lesion (HRL)—such as atypical ductal

hyperplasia (ADH), ductal (DCIS) or lobular carcinoma in-situ (LCIS). The upgrade rate (from core to excision) is reported to lie between 1% and 3% with no associated HRL and 1%–14% in the presence of an HRL. Surgical excision (which could include vacuum assisted core biopsy) may be recommended for an HRL, size >1 cm or when there are discordant histological and mammographical findings, and observation appropriate when there is absence of the latter and when the lesion has been widely sampled, for example, following ≥ 14 -gauge needle core biopsy (NCB) and/or >12 core biopsy sampling.³⁶ Vacuum assisted core biopsy revealing an RS/CSL is reliable for excluding malignancy when there is no associated atypia, and radiological and histological findings are concordant. In this setting, imaging-based follow-up is appropriate.⁴⁴ Rhaka *et al*⁴⁵ found that the overall upgrade rate to carcinoma on excision following core biopsy of a high-risk RS/CSL was nearly 25% and was highest for ADH in which the upgrade rate was similar to that of ADH not occurring in the context of an RS/CSL. They concluded that the management of RS/CSL should be based on a concurrent atypical lesion detected at core biopsy.

RS/CSL, in common with other SL/BLWS and other lesions (eg, papillomata, NA and adenomyoepithelioma), also show an association with low-grade metaplastic carcinoma including LGASC, spindle cell and fibromatosis-like metaplastic carcinoma,^{24 26 29–33} particularly LGASC, which is interesting given the similarity of ASP in benign SL and LGASC.^{1 27}

Using microdissection, RS have been shown to harbour areas that are clonal and neoplastic.⁴⁶ Jacobs *et al*⁴⁷ demonstrated similarities in mRNA expression for several factors involved in vascular development, in RS and carcinoma (but only invasive ductal carcinoma), suggesting a similar disturbance in epithelial-stromal interaction is present in RS and invasive breast carcinoma. Wolters *et al*⁴⁸ demonstrated activating PIK3CA mutations in 63.6% of macrodissected RS but stated that the frequency may reflect the morphology of the associated epithelium (eg, UDH which harbours similar mutations) rather than its underlying architecture or context such as an RS or benign papilloma. More recently, NGS of microdissected ASP from cellular, early RS/CSL has demonstrated clonality, also in the form of recurrent PIK3CA mutations.²⁷

IE is a term introduced by Azzopardi¹⁴ for a lesion he agreed was likely synonymous with a RS/CSL under its various epithets. The definition of IE has evolved over time, since inception of the term, with Eusebi and Millis⁴⁹ regarding it different to an RS, stating that it differed from the latter in that it is non-stellate and cellular, having an epitheliosis (UDH) component including Heliod bodies (as previously described in UDH by Tavasoli *et al*⁵⁰) and a scleroelastic component resembling LGASC (describing ASP). The concept has further evolved with Eberle²⁶ reporting that the lesion contains a UDH-like proliferation that lacks peripheral myoepithelial cells, and demonstrating clonality in the form of recurrent PI3K pathway mutations (PIK3CA in seven cases and PIK3R1 in one case) and clonally related IE, DCIS and LGASC in one case. They pointed out that the rarity of diagnosis of IE was due to most pathologists classifying it as an RS/CSL, and that IE may represent the most proliferative end of the spectrum of these lesions. IE is proposed to form a spectrum with TCCR, which also has a hyperplasia-like phenotype.^{20 21 51–55}

SCLEROSING PAPILLOMA

IP is a common breast lesion, histologically composed of frond forming/branching, intraductal projections of bilayered

Figure 2 Sclerosing papilloma. (A) Sclerosing papilloma, needle core biopsy (H&E low-power overview). (B) Adenosquamous proliferation (ASP) with dense sclerotic background (H&E medium power). (C) Dual CK5 (red) and p63 (brown) immunohistochemistry. (D) Coexpression of CK5 and p63 by ASP (CK5/p63 dual staining—medium power). (E) Myosin heavy chain—muddy blurry staining of desmoplastic reaction. (F) ASP is oestrogen negative.

epithelium and myoepithelium that are supported by stromal cores. They may occur in dilated ducts, cysts ('papillary cystadenoma') or be solid ('DAs'). Various epithelial and myoepithelial changes may be seen including apocrine metaplasia, UDH, myoepithelial hyperplasia, sclerosing changes (SP), lobular and ductal carcinoma in-situ.^{36 56} The upgrade rate to cancer from NCB to excision for benign papillomata is between 2% and 9%, and for papillomata with atypia is 21%–37%. Following NCB diagnosis, surgical excision is appropriate for lesions with atypia, and may be appropriate for benign papillomata in individuals >age 55, lesions >10 mm, with associated ipsilateral breast cancer or if its upgrade would alter management.³⁶ A proportion of IP harbour PIK3CA/AKT pathway mutations (figure 2).^{57 58}

Sclerosing changes in a papilloma (SP) are not uncommon and there is morphological and immunohistochemical overlap with other SL/BLWS. Their overlap with RS/CSL is documented and they have previously been considered a single entity.^{5 20} Sclerosis distorts and may obliterate the papilloma in time. Myoepithelium may be markedly attenuated to absent and squamous metaplasia noted. The infiltrative appearance, within and/or at the periphery of the papilloma may mimic low-grade metaplastic carcinoma.^{20 56 59} ASP is a feature of SPs and its presence seems less apparent in more sclerotic, distorted lesions, similar to the evolution seen with RS/CSL. It may be seen within the core of the papilloma or at its base. If carcinoma cannot be excluded, excision biopsy would typically be performed.

DA: WITH SCLEROSIS

DA is a rare tumour that usually presents in the sixth decade of life as a solitary palpable mass, but it may be multiple.⁶⁰ Although regarded as a distinct lesion by the WHO,⁶⁰ it shows considerable overlap with various other SL/BLWS. Histologically, it resembles

Figure 3 Breast lesions with sclerosis—other. (A) Ductal adenoma (H&E full section scan). (B) Ductal adenoma—sclerosing architecture (H&E medium-power). (C) Nipple adenoma (H&E full section scan). (D) Nipple adenoma—sclerosing architecture with adenosquamous proliferation visible (H&E full section scan). (E) Subareolar sclerosing duct hyperplasia (H&E full section scan). (F) Subareolar sclerosing duct hyperplasia—sclerosing architecture (H&E medium-power).

an IP devoid of the typical arborescent fronded architecture, and resides within a fibrous walled ductal space, of variable calibre, or appears to have outgrown one. Lesions may be single or multifocal, may resemble SP and RS/CSL, lesions sharing the presence of ASP, and can be associated with duct ectasia.^{18 61} In view of mixed histological features in DA, Page and Anderson⁶² regarded them as ‘muddling lesions’ and in their day-to-day practice reported them as ‘sclerosing and adenotic variants of papilloma, nodular sclerosing adenosis or CSL, depending on which they most resemble’. Missense mutations of AKT1, GNAS and PIK3CA have been previously demonstrated.⁶³ It measures 0.5–5 cm (average 0.82 cm) and excision is the generally recommended treatment due to mimicry of carcinoma—clinically, radiologically and on core biopsy. Reported associations with malignancy may be coincidental rather than representing malignant transformation (figure 3A,B).⁶⁰

NA: SCLEROSING PAPILLOMATOSIS PATTERN

NA is the WHO⁶⁴ recognised term for the lesion described in 1955 by Jones,⁶⁵ as ‘FP of the nipple ducts’, typically clinically presenting with nipple enlargement, erythema, erosion and/or discharge and corresponding histologically to a polymorphous pattern of papillary and adenomatous growth. The same entity has previously been called adenoma of the nipple⁶⁶ and is not the same entity as syringomatous adenoma of the nipple (currently termed ST).⁶⁷ Rosen and Caicco²² described four relatively distinct categories, in three, one feature was dominant or exclusively present and in the fourth there were mixed features. Categories described were: sclerosing papillomatosis pattern,

papillomatosis (papilloma and UDH) pattern, adenosis pattern and mixed proliferative pattern. Apocrine cysts and squamous cysts are common features of all subtypes. The sclerosing papillomatous pattern of NA comprises ASP and/or sclerosis associated with papillomatous change, and is most likely to be confused with other SL/BLWS, including ST or the rare occurrence of LGASC in the nipple (although the two latter lesions may indeed be synonymous).^{24 25} Similar to other benign proliferative and sclerosing breast lesions, activating PIK3CA mutations are very common in NA and important in its pathogenesis. In addition, KRAS and BRAF mutations may also be important.⁶⁸ Lesions are most common in the fifth decade, range from 0.5 cm to >4 cm and may recur if incompletely excised (figure 3C,D).⁶⁴

SUBAREOLAR SCLEROSING DUCT HYPERPLASIA

SSDH was described by Rosen²³ for a central or subareolar lesion, equivalent to NA/FP occurring in the nipple or RS/CSL occurring in peripheral breast tissue. It was regarded as a benign lesion of which excision alone was adequate treatment. It is essentially a form of SP. Clinical presentation is as a firm or hard tumour, beneath the nipple and/or areola or close to the areola, which may be accompanied by nipple discharge and/or nipple retraction. Lesions average 1.2 cm (0.3–3 cm) in size with a broad age range (average around 60 year). The histology is of a sclerosing papillary lesion with moderate UDH and desmoplasia within and surrounding the lesion with entrapped glandular elements with a variable infiltrative appearance. Focal keloid-like stroma and diffuse fibroelastosis are described as well as apocrine metaplasia and squamous metaplasia. At the periphery, CK5/6 expression may be more prominent and myoepithelial cells focally not demonstrable. The description essentially relates to the presence of ASP and associated sclerosis. Significant co-existing lesions within SSDH may include LGASC, DCIS, LCIS and ADH. Recurrence is not recorded after excision.^{23 69–71} It is not a specific WHO recognised entity and in day-to-day practice may be reported as a variant of NA, SP or RS/CSL dependent on the predominant histological feature (figure 3E,F).

SYRINGOMATOUS TUMOUR AND LOW-GRADE ADENOSQUAMOUS CARCINOMA

ST is the WHO⁷² recognised term for the entity Rosen⁶⁷ introduced as syringomatous adenoma of the nipple. It is likely included in previous series by Handley and Thackray⁶⁶ and Doctor *et al.*⁷³ ST is rare and is regarded as a locally infiltrative, nipple-based counterpart of the also rare LGASC, which typically arises within breast parenchyma. They may measure 0.5 cm to >4 cm. Local recurrence may follow incomplete excision.⁷² They are rarely metastasizing,⁷⁴ and can present bilaterally and be locally destructive.⁷⁵ Distinguishing features from LGASC may include a less common occurrence of neoplastic spindle cells, less densely cellular stroma and lack of peripheral lymphoid aggregates (figure 4).⁴¹

LGASC was described by Rosen and Ernsberger⁷⁶ and the original series of 11 cases was expanded and followed up by Van Hoesen *et al.*²⁹ They demonstrate local infiltration and rarely metastasise, generally when large (>3 cm), following multiple recurrence or high-grade transformation. LGASC has a distinctive histological appearance and comprises variably compressed tubules that may be lined by columnar or squamous cells with a variable outer layer of myoepithelial-like cells that may merge with squamous elements and may form tadpole-like/syringoid extensions, set within a desmoplastic background that may contain lymphoid aggregates.^{1 29 33 41 76} The age at presentation

Figure 4 Syringomatous tumour of the nipple (ST) and low-grade adenosquamous carcinoma (LGASC). (A) ST. Skin is absent (top) (H&E—low power overview scan). (B) Adenosquamous proliferation (ASP)-type invasive tumour predominates—permeating in between lactiferous ducts (H&E low-power). (C) LGASC. Note lymphoid aggregate on left (H&E low-power). (D) LGASC. ASP-type infiltrating, neoplastic ducts within desmoplastic stroma predominate (H&E medium-power). (E) LGASC. Outer cells and squamoid cells variably express p63 (medium power). (F) LGASC. Myoid markers highlight variable myoepithelial-like cells (particularly in transitional areas) and particularly stromal myofibroblasts (calponin—medium power).

is broad (19–85 years) and size varies from 0.5 cm to 80 cm, but is mainly <5 cm.¹

The immunohistochemical profile of LGASC is characteristic, but not unique.^{1 25 33 41 77 78} Geyer *et al*⁷⁸ demonstrated that LGASC is characterised by complex genetic profiles, including epidermal growth factor receptor (EGFR) amplification. One case has previously occurred in a BRCA1 germline carrier.⁷⁹ It has been shown to harbour PI3K pathway mutations, typically PIK3CA,^{26 27} but not TP53 mutations.²⁸

LGASC are often noted in association with benign breast lesions, most typically SL/BLWS.^{24 26 29–33} Benign ASP-rich SL/BLWS seem to form a morphological spectrum with LGASC. Morphology is most helpful to distinguish a benign SL/BLWS (eg, RS/CSL) from LGASC such as extent of ASP and degree of infiltration, for example, in an RS/CSL-like lesion, invasion of ASP beyond the corona into breast parenchyma or within predominant desmoplastic stroma.^{1 2 41} In reference to RS/CSL, immunohistochemical studies are non-discriminatory and lymphocytic infiltration is common in early proliferative phase lesions, although perhaps not as prominent lymphoid aggregates as described in LGASC.¹ LGASC may indeed represent an indolent carcinoma whose non-obligate precursor may be identified in RS/CSL, at least in a subset of cases.²⁸

The distinction between ST and LGASC is controversial with seemingly histologically identical lesions called benign if located in the nipple region, and malignant if arising within breast parenchyma. Moreover, LGASC has also been reported in a pure nipple location.²⁴ Indeed, in a detailed study, Boecker *et al*²⁵ provided evidence supporting that they are one in the same lesion usually occurring in different locations. As Kanthan and Senger⁸⁰ state ‘a single entity with two homes’. Boecker *et al*²⁵ stated that ST and LGASC were identical or near identical lesions and contained p63, CK5 and CK14 positive (+) cells (generally at the periphery of cell groups) from which a (CK10 and p63 positive) squamous lineage and a (CK8/18+, p63–) glandular lineage arise. Immunohistochemically, identical progenitor cells (p63+/CK5+/CK14+) were demonstrated in normal breast duct epithelium of the nipple and/or large breast ducts, supporting that ST and LGASC might both arise from such progenitor cells and both be of breast duct origin (as opposed to ST alternatively being of sweat duct origin). Histologically, both ST and LGASC showed both a luminal glandular and squamous immunophenotype, and an outer myoepithelial-like layer expressing only p63, CK5 and CK14. Myoepithelial differentiation was defined by expression of p63 and/or the basal keratins CK5 and CK14, and myoepithelial marker SMA. Both ST and LGASC were associated with other lesions in some cases, with ST associated with either a papilloma or ‘adenomatous adenoma’ and LGASC associated with sclerosing adenosis or IP. Occasional myoepithelial cells were seen in ST and LGASC in cases associated with benign lesions, and transitional areas apparent. In summary they stated that in contrast to reports in the literature, the presence of lymphoid aggregates was not found to be a distinguishing feature between ST and LGASC, and myoepithelial markers such as SMA were not constitutively expressed. An encompassing term ‘syringomatous adenomatous tumour’ may be appropriate.²⁵ Both lesions are similarly adequately treated by wide local excision ensuring clear margins.

DISTINCTION BETWEEN LESIONS

Some of the lesions described lesions are WHO recognised entities, including RS/CSL, NA and DA. Lesions such as IP and NA as entities, are not categorised as SL, but have a sclerosing variant/subtype with sclerosis (BLWS). In common, they share an association with ASP, which likely is the cause of sclerosis and distortion of the ‘base’ lesion. Distinguishing between a SL/BLWS with prominent ASP and a LGASC is challenging, and their distinction is subjective. However, a lesion may be best regarded as a LGASC when the ASP forms a distinct tumoural mass with ASP in a pure desmoplastic stroma and moreover when the latter prominently invades adipose tissue. Despite overlapping features, diagnosis rests on a combination of anatomical site and predominant histological feature.²⁷ A basic outline of lesions and distinguishing features are listed in table 1. A tree diagram aiding distinction of lesions is provided (figure 5).

CONCLUSIONS

SL/BLWS of the breast form a diverse array of lesions, and often appear histologically similar to one another with the final diagnosis determined by anatomical location or predominant histological feature. A common thread is the sclerosing component, which appears to be secondary at least in most instances, to a common element of ASP, the associated desmoplasia of which appears to distort and modify the base lesion (fibrocystic disease, papilloma, UDH/UDH-like proliferation, etc). The ASP, as is classically seen in RS/CSL, seems to involute and disappear over

Table 1 Sclerosing lesions and breast lesions with sclerosis (SL/BLWS), characterised by adenosquamous proliferation or equivalent

Details	Radial scar/complex sclerosing lesion (RS/CSL)	Infiltrating epitheliosis (IE)	Sclerosing papilloma (SP)	Ductal adenoma—with sclerosis (DA)	Nipple adenoma—sclerosing papillomatosis pattern (NA)	Subareolar sclerosing duct hyperplasia (SSDH)	Syringomatous tumour (ST)	Low-grade adenosquamous carcinoma (LGASC)
Nature	Benign	Benign—variant of RS/CSL	Benign	Benign	Benign	Benign	Generally indolent, locally infiltrative	Generally indolent, rarely metastasizing
Localisation	Breast parenchyma (central or peripheral)	Breast parenchyma (central or peripheral)	Breast parenchyma (central or peripheral)	Breast parenchyma, (central or peripheral)	Nipple	Beneath nipple or areola	Nipple, may invade breast parenchyma if large	Breast parenchyma, rarely involves nipple
Size	Varies, RS <10 mm, CSL >10 mm	Varies	Varies	Varies	Varies	Varies	Varies	Varies
Age at presentation	Broad range	Broad range	Broad range	Broad range, but mainly sixth decade	Broad range	Broad range, but mainly sixth decade	Broad range	Broad range
Presentation	Radiological abnormality or mass if large	Radiological abnormality or mass if large	Typically a radiological abnormality	Palpable mass and/or a radiological abnormality	Ulceration, nipple discharge, visible lesion or palpable thickening of nipple	Palpable mass and/or a radiological abnormality	Often as a palpable mass	Radiological abnormality or palpable mass if large
Histological architecture	Stellate, floral architecture, particularly if smaller (RS), larger lesions (CSL), may be more complex and disorganised	Non-stellate, irregular outline, infiltrative	May be confined to a duct or duct system or extend beyond duct, rounded to variably distorted and sclerotic	Rounded and contained within a duct or appearing to infiltrate into sclerotic periductal stroma	Mass forming, rounded to irregular, infiltrative appearing periphery	Irregular outline, central scarring	Irregular outline, infiltrative, typically confined to dermis and nipple stroma	May appear stellate and RSL like, typically has an irregular outline with invasion of breast parenchyma (adipose tissue)
Basic histological features	Smaller lesions (RS) show central nidus surrounded by a rosette-like corona comprising proliferative or fibrocystic disease. CSL may show multiple niduses. Nidus in early lesions contains ASP in mucoid, inflammatory stroma; late lesions characterised by hypocellular, fibroelastic nidus/zones	Predominant features is UDH/UDH-like proliferation with jagged edges an often proliferative growth pattern, variably accompanied by ASP (miniature LGASC-like proliferation)	Intraduct papilloma is the base lesion, distorted by sclerosis associated with variable ASP	Solid intraduct papilloma-like lesion is the base lesion, with variable sclerosis and distortion. Can appear stellate in appearance (eg, if sclerosis occurs centrally)	Papillomatosis pattern / florid UDH within ducts is base lesion, with variable sclerosing distortion	Variable papillary, ductal and stromal proliferation, central sclerosing papillary proliferation, irregular extension into small ducts at the periphery, small cysts with hyperplasia seen at the periphery of some lesions	Infiltrating ducts with squamous and glandular differentiation within a desmoplastic background. May show more cellular, spindle cell rich stroma than ST and lymphoid aggregates, but disputed	Infiltrating ducts with squamous and glandular differentiation within a desmoplastic background. May show more cellular, spindle cell rich stroma than ST and lymphoid aggregates, but disputed
Prominence of ASP or equivalent proliferation	Characteristic within nidus of early RSL, diminished or absent in end-stage/late RSL	Varies, may be inconspicuous	Varies, may be more visible in 'early' lesions	Varies, may be more visible in 'early' lesions	Varies	Varies, may be more visible in 'early' lesions	Predominant feature	Predominant feature
Pattern of ASP or equivalent proliferation	Confined to nidus in early RSL. Diminished or totally absent in late RSL	Not confined to a central nidus, may be multiple. With prominent sclerosis it may be inconspicuous (essentially CSL-like pattern with UDH/UDH-like process predominating)	Within centre or periphery of lesion, but with prominent sclerosis it may be inconspicuous	Within centre or periphery of lesion, but with prominent sclerosis it may be inconspicuous	May be focal or scattered throughout lesion, but with prominent sclerosis it may be inconspicuous	May be central within lesion, but with prominent sclerosis it may be inconspicuous	Infiltrative within dermis and nipple stroma	Infiltrative within breast parenchyma. Can show limited infiltration and mimic an early, proliferative phase RSL

Continued

Table 1 Continued

Details	Radial scar/complex sclerosing lesion (RS/CSL)	Infiltrating epitheliosis (IE)	Sclerosing papilloma (SP)	Ductal adenoma—with sclerosis (DA)	Nipple adenoma—sclerosing papillomatosis pattern (NA)	Subareolar sclerosing duct hyperplasia (SSDH)	Syringomatous tumour (ST)	Low-grade adenosquamous carcinoma (LGASC)
Immunohistochemistry	ASP is triple negative for ER, PR and HER2, shows inconsistent presence of myoepithelial-like cells with myoid markers (eg, SMA, myosin, calponin), shows coexpression of high molecular weight cytokeratins (eg, CK5/6) and p63. Myofibroblastic stroma expresses myoid markers, typically cuffing epithelium. Corona shows intact myoepithelial layer and heterogeneous ER and PR expression	UDH and UDH-like proliferation expresses CK5/6. Myoepithelial cells generally absent from UDH-like proliferation, often lacking expression of p63 and myoid markers. ASP when present stains as described earlier	Bi-layer of epithelium and myoepithelium demonstrable, heterogeneous ER and PR expression. UDH expresses CK5/6. ASP stains as described earlier. Sclerosing areas show inconsistent myoepithelial component	Essentially same as sclerosing papilloma	Essentially same as sclerosing papilloma	Essentially same as sclerosing papilloma. Myoepithelial cells less demonstrable at lesions periphery	Triple negative for ER, PR and HER2. Luminal glandular and squamous immunophenotype, and an outer myoepithelial-like layer expressing p63, CK5/6 and CK14, but generally not myoepithelial-like layer expressing p63, CK5/6 and CK14, but generally not myoid markers. The latter are expressed by desmoplastic stroma which may form a lamellar cuff around tumour, or form sheets. Some spindle cells may express cytokeratin and p63	Triple negative for ER, PR and HER2. Luminal glandular and squamous immunophenotype, and an outer myoepithelial-like layer expressing p63, CK5/6 and CK14, but generally not myoid markers. The latter are expressed by desmoplastic stroma which may form a lamellar cuff around tumour, or form sheets. Some spindle cells may express cytokeratin and p63
Molecular genetics	PIK3CA mutations	PIK3CA and PIK3R1 mutations	PIK3CA/AKT pathway mutations (P—sclerosis unspecified)	AKT1, GNAS and PIK3CA mutations	PIK3CA, KRAS and BRAF mutations	Unknown	Unknown	PIK3CA mutations and EGFR amplification
Treatment	Excision if large, symptomatic or associated high-risk lesion present, otherwise radiological surveillance	Excision if large, symptomatic or associated high-risk lesion present, otherwise radiological surveillance	Excision if large, symptomatic or associated high-risk lesion present, otherwise radiological surveillance	Excision if large, symptomatic or associated high-risk lesion present, otherwise radiological surveillance	Excision	Excision if large, symptomatic or associated high-risk lesion present, otherwise radiological surveillance	Excision	Excision

ASP, adenosquamous proliferation; CSL, complex sclerosing lesion; EGFR, epidermal growth factor receptor; ER, oestrogen receptor; PR, progesterone receptor; RS, radial scar; UDH, usual ductal hyperplasia.

Figure 5 Aide memoir for the classification of sclerosing lesions/breast lesions with sclerosis (SL/BLWS). DA, ductal adenoma; FCC, fibrocystic change; FP, florid papillary change/papillomatosis; IE, infiltrating epitheliosis; IP, intraduct papilloma; LGASC, low-grade adenosquamous carcinoma; MP, micropapilloma; NA-SPP, nipple adenoma-sclerosing papillomatosis pattern; RS/CSL, radial scar/complex sclerosing lesion; SASDH, subareolar sclerosing duct hyperplasia; SP, sclerosing papilloma; ST, syringomatous tumour; UDH, usual ductal hyperplasia.

time. It may be a prominent to inconspicuous, or even absent component in any one lesion at the time of histological assessment. SL/BLWS have an inherent neoplastic risk with 'common' carcinomas (in-situ or invasive) arising from the non-scleroelastic component (UDH, etc) due to its inherent neoplastic risk regardless of its association with a sclerosing lesion and low-grade metaplastic carcinoma, particularly LGASC, perhaps derived from persistent growth of ASP characterising the sclerosing component. Distinction between the various entities may be difficult and any one lesion may fit several categories. Difficult-to-categorise lesions are typically adequately treated by local excision with clear margins.

Take home messages

- ▶ Adenosquamous proliferation of the breast is a key component of sclerosing lesions and breast lesions with sclerosis.
- ▶ ASP in SL/BLWS is phenotypically similar to the neoplastic proliferation characteristic of syringomatous tumour and low-grade adenosquamous carcinoma.
- ▶ ASP may represent a non-obligate neoplastic precursor lesion for low-grade metaplastic carcinoma, eg, LGASC.
- ▶ Distinguishing between SL/BLWS with prominent ASP and LGASC can be diagnostically challenging and their distinction may be based on the extent of the ASP.

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