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Review Article

Histopathological and Molecular Features of the Mammary Sclerosing Adenosis Lesions and Their association with breast carcinoma: Review of literature

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Abstract

Sclerosing adenosis (SA) is one of the findings seen in breast biopsies both in symptomatic and asymptomatic patients. Accurate diagnosis of this lesion is sometimes challenging for pathologists and radiologists. The lesion is characterized by proliferation of irregular glands with excess sclerosis in the surrounding stroma giving the lesion the features of invasive carcinomas. Will SA evolve into carcinoma? How long will it take for this transformation to occur? Can we distinguish between lesions that will undergo malignant transformation and those won't? These are all questions that have been raised about SA for years. Management of SA is not a straightforward decision; it differs from patient to another according to several factors. The following review article shed light on the recent updates about SA of the breast, its morphological histopathological characteristics, features that distinguish it from malignant tumors, radiological features, molecular mechanisms underlying this process and its management.

Keywords: Sclerosing adenosis, radial scar, breast carcinoma, risk

Introduction

Sclerosing Adenosis (SA) is one of the benign proliferative lesions sometimes seen in breast biopsies. The lesion is rarely symptomatic and therefore is most detected at screening mammography. When it is accompanied by symptoms it is usually in the form of pain confined to a certain area of the breast. This pain worsens immediately before the menstrual period and improves afterward [(1)]. SA can be presented as an ill–defined breast mass which may be fixed to surrounding tissues. The mass is usually solitary ranging in size from 0.5 to 5 cm. In rare cases it can be multifocal and bilateral.

SA is estimated to occur in up to 28 % of all benign breast biopsies. The lesion is most common in women aged 45–55 years and is more common in women with a strong family history of breast cancer compared with women with no family history and is also more common in women who used hormonal replacement therapy [(2)].

The lesion is characterized by proliferation of mammary lobules with variable degrees of sclerosis. Sometimes, the sclerosis in SA is excessive resulting in what is called radial scar OR complex sclerosing lesion which may produce a mass known then as nodular sclerosing adenosis [(3)].

SA is categorized with the benign proliferative lesions of the breast. The exact etiology of SA is debatable. Some authors linked benign breast diseases to dynamic hormonal changes at a chronobiological rhythms; daily, menstrual, and seasonal [(4)]. Others consider it as one of the manifestations of fibrocystic disease of the breast due to its high prevalence on top of fibrocystic changes of the breast [(5)]. Others relate SA to some form of tissue reaction to exposure to a previous trauma. Trauma induces elastosis in the breast tissue which then distorts the lobular component of the breast in the area exposed to trauma [(6)].Other authors considered SA, Complex SA and radial scar one lesion that goes through dynamic phases which starts by inflammation. This inflammation will have a cellular phase that can be described as the proliferative phase then sclerosis increased resulting in complex sclerosing adenosis then this sclerosis matures forming the radial scar which will then have a characteristic star shape due to contraction of the scar tissue [(7)].

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The possibility of systemic hormonal imbalance such as hypothyroidism was found to be high in benign proliferative breast diseases but there is no proof for a causal link [8]. No association with cigarette smoking [9], alcohol consumption [10] or physical activity [11] was detected.

Normal histological appearance of breast lobule

At the microanatomy level, the normal breast is made up of 15–25 secretory lobes embedded in adipose tissue. Each of these lobes composed of a group of acini which in turn empty into ducts. The normal acini (also commonly known as lobules or simply glands) are lined by cuboidal, or low columnar epithelial cells, and are surrounded by myoepithelial cells [12] (figure–1). Due to several factors –most commonly exposure to excess estrogen. This normal mammary lobular structure underwent hyperproliferation leading to a spectrum of lesions known as hyperproliferative lesions of the breast. These lesions include ductal hyperplasia (with or without atypia), lobular hyperplasia (with or without atypia) and sclerosing adenosis.

Histopathological features of Sclerosing Adenosis

SA was originally defined as those lesions characterized by cellular lobulocentric proliferation of both epithelium and myoepithelium cells. The lesion is therefore composed of enlarged lobules, containing distorted, crowded compressed acini, associated with fibrosis (figure–2) [13]. Sometimes, the sclerosis in SA is excessive resulting in what is called radial scar OR complex sclerosing lesion which may produce a mass known then as nodular sclerosing adenosis [3]. The incidence of complex SA is difficult to assess in the general population. In a study examined autopsies from breast tissue, the prevalence of this lesion was found to range from 14% to 28% [5, 6] and to be multicentric in 67% and bilateral in 43% of examined autopsies [5]. Using screening methods on the population, rates between 0.05% and 0.065% have been reported [14, 15].

SA can be found alone or associated with other proliferative changes such as ductal hyperplasia or lobular hyperplasia. The frequency of SA reaches 43% when it arise on top of fibrocystic changes in the breast and decreases to 17% when there is no fibrocystic changes [5]. Most women with SA (84.7%) were also found to have columnar cell alterations within the SA lesions [2].

Clinical significance of sclerosing adenosis:

SA is sometimes challenging in diagnosis. Differentiating it from invasive carcinomas during histopathological evaluation, especially in core needle biopsies, is not easy and needs experience. The proliferative glandular structures in SA are compressed, elongated, and distorted due to the accumulation of stromal collagen. This alteration makes the gland's shape irregular, narrow and collapsed. Adding to this the typical radial arrangement of the lesion, this will collectively create an impression of invasive carcinoma (Figure 3 A&B) [16, 17]. One of the main distinguishing features that identify SA in excisional breast biopsies, is that each of the individual glands in SA is composed of both epithelial cells and surrounded by myoepithelial cells, with frequent hyperplasia of the latter. Preservation of the myoepithelial layer is a clue to the benign nature of the lesion. Unlike the homogeneous

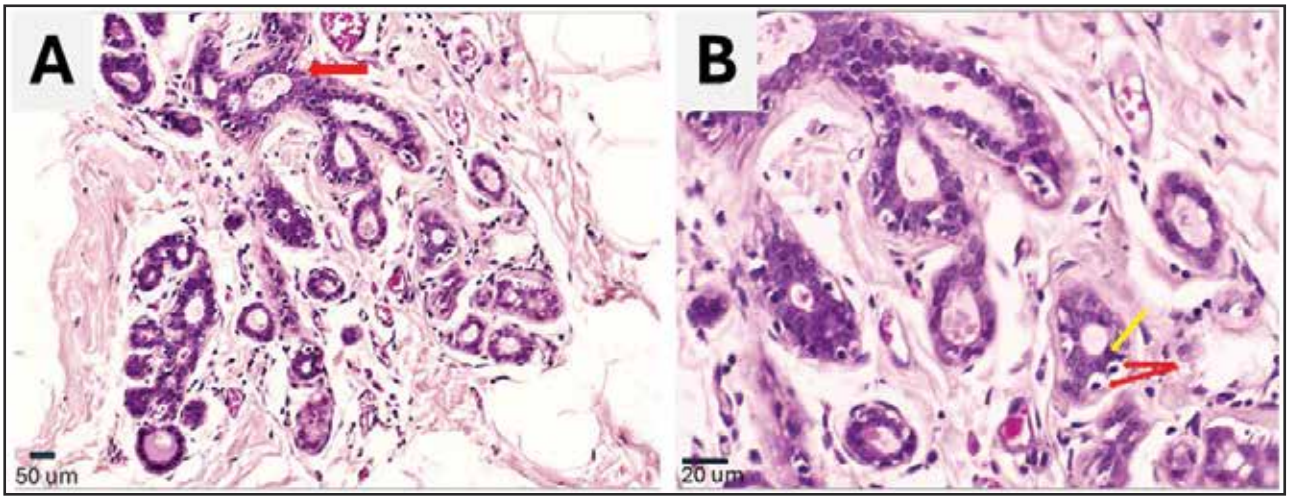


Figure 1. Tissue section from a normal mammary lobule stained with hematoxylin and eosin. **[A]** Each unit is composed of a central duct (arrow) surrounded by multiple acini x10. [B] a higher magnification of A showing the normal cells in the acini; peripheral myoepithelial cells (red arrows) and an inner columnar secretory cells (yellow arrow) x40.

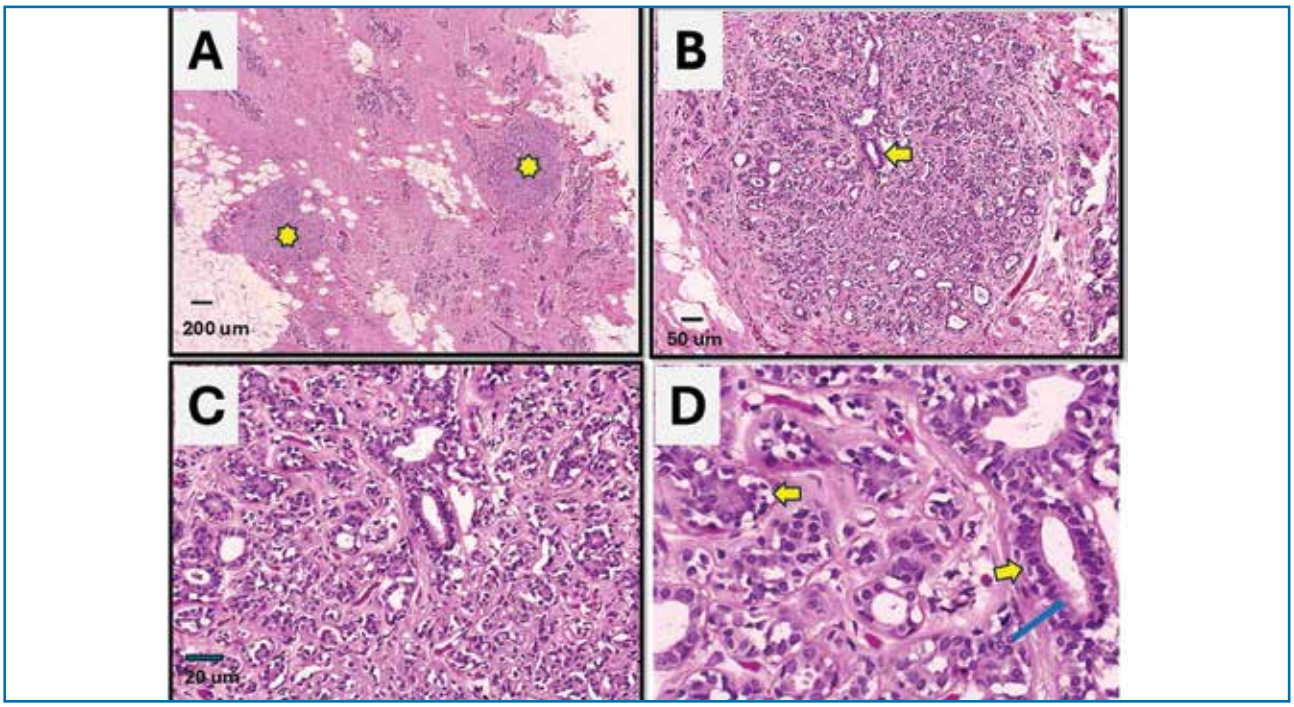


Figure 2. Tissue sections stained with hematoxylin and eosin from an excisional biopsy of a sclerosing adenosis lesion of the breast. (A) there are two foci (stars) appear as nodules at low magnification (x2.5). (B) the nodule on the right at x10 magnification shows a central duct (arrow) with numerous proliferating acini around. The size of the lobule is enlarged compared to lobules in normal breast. (C) Higher magnification from B showing central duct with the surrounding acini some of which are distorted and irregular mimicking malignant glands x20. (D) Higher magnification of C showing the proliferating acini with two types of cells; peripheral myoepithelial cells which are characterized by being plump cells with clear cytoplasm (yellow arrows) and inner columnar or cuboidal cells (blue arrow) (x40).

epithelial proliferation of luminal cells seen in usual ductal hyperplasia, SA combines the proliferation of epithelial, myoepithelial, and mesenchymal cells [18]. This mixture of cells is absent in malignant glands. The presence of myoepithelial cells at the periphery of the proliferating glands can be seen in the hematoxylin–stained tissue sections and can be confirmed by immunohistochemical markers for myoepithelial cells such as smooth muscle actine (Figure–3 C&D), calponin, smooth muscle myosin heavy chain, p63, CD10, cytokeratin 5/6, and p75 [19, 20].

Although the availability of these numerous myoepithelial markers, they differ in their sensitivity, specificity, and ease of interpretation. Moreover, some of these markers are also positive for the stromal cells such as the myofibroblasts and smooth muscle layer of the vessels. This should be taken into consideration while interpreting the staining results. It was also reported that the myoepithelial cells undergo phenotypical changes in SA lesion when compared with myoepithelial cells in normal mammary lobules, some of the markers showed reduced expression. The robust marker was found to be the muscle actin which was uniformly reliable in staining of myoepithelial cells in 100% of tissues both in SA lesions and in normal lobules [20]. It was recommended to use a panel–based approach of 2 or more myoepithelial markers to get the best reliable marking for presence or absence of myoepithelial cells [21].

One of the common finding in pathological practice is the associated lesions within SA. Atypical apocrine changes which can be misdiagnosed as apocrine ductal carcinoma in situ, atyical hyerlasia, ductal carcinoma insitu or even invasive carcinoma were all reported with SA. A considerable percentage of biopsies with SA, have a focus of carcinoma which is usually low grade or tubular carcinoma within the lesion. Diagnosis of this focus can be missed during examination [22]. SA lesions should then be examined with caution and with examination of several deeper sections from the lesion.

Lobular carcinoma in situ within SA was also reported. This type of carcinomas exhibit patterns akin to invasive lobular carcinoma, thus leading to potential misdiagnosis [23]. One of the essential distinguing features between SA and carcinomas is the overall architecture of the lesion using microscoic examination by the low magnification lenses. Foci of sclerosing adenosis, with or without carcinoma in situ, have dilated ductules peripherally, and narrow ones centrally, whereas infiltrating carcinomas do not show this overall organization [24].

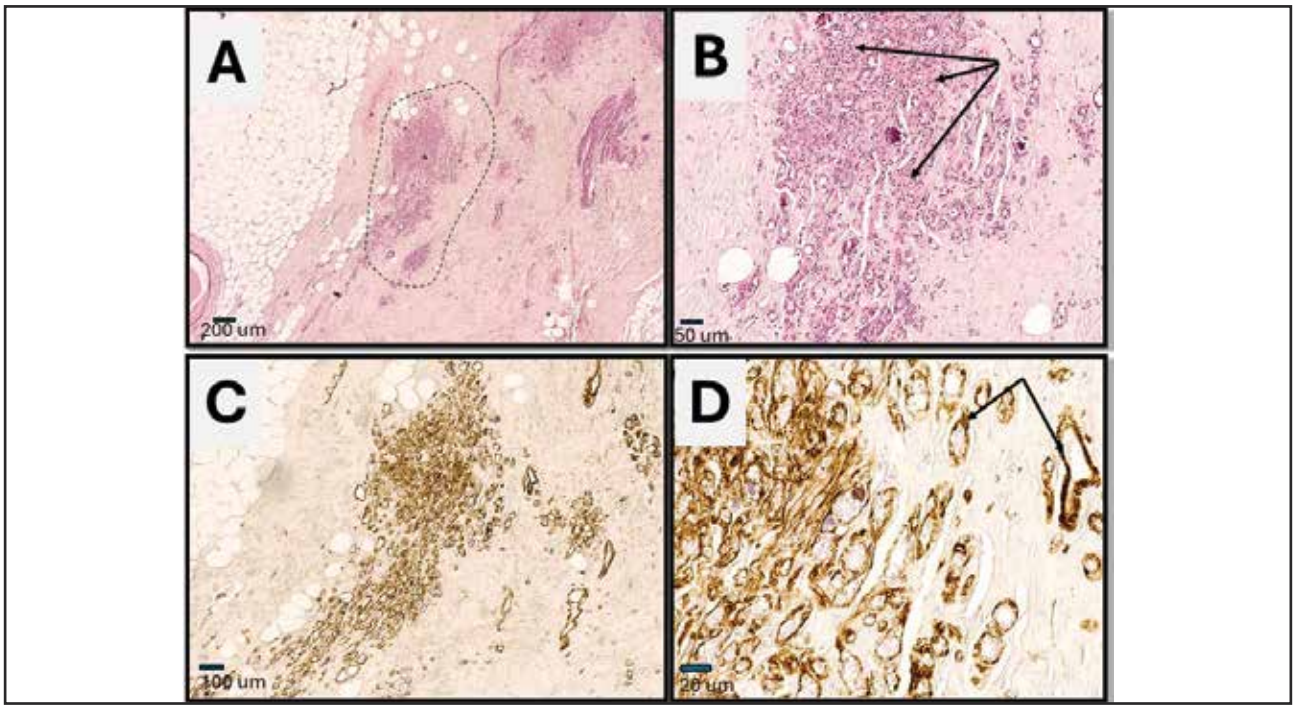


Figure 3. [A] Tissue section from sclerosing adenosis (within the dashed lined circle) stained with H&E. [B] Higher magnification from A showing the compressed irregular glands with intervening fibrosis x10. [C] is the same section stained with Smooth muscle actin, a marker for the myoepithelial cells x5. [D] is a higher magnification of C showing that each of the glands is surrounded by a layer of smooth muscle actin–positive myoepithelial cells which indicates the benign nature of the lesion and excludes malignant glands X40.

Sclerosing adenosis in needle and cytology smears

If the diagnosis of SA is challenging in the assessment of excisional breast biopsies, it is more difficult in the assessment of fine needle aspiration cytology smears. Fine needle aspiration cytology findings cannot reach an unequivocal diagnosis. SA is included under what is called the "grey zone" lesions in breast diagnosis. In fine needle aspiration, SA will yield cellular smear with cohesive clusters and scattered epithelial cells. Due to the proliferative nature of cells, nuclei will show variable degrees of nuclear pleomorphism with the possibility of the presence of naked nuclei. Acinar formation is commonly mixed with stromal fragments and benign epithelial cell clusters in the background. All these features may lead to a false diagnosis of a malignant lesion [25]. Confirmation by excisional biopsy becomes mandatory in difficult cases.

Diagnosis of sclerosing adenosis by imaging

Diagnosis of SA by imaging (mammography, ultrasonography (US) and magnetic resonance imaging (MRI)) is also challenging. The majority of SA lesions shows distortion or calcifications on mammograms, low echo–level nodules with heterogenous echo on US, and mass–like lesions with or without star shape on enhanced MRI. Diagnostic difficulty is worse in cases of nodular SA which shares histopathological and imaging features mimicking malignant neoplasms making its diagnosis a challenge [3]. Those lesions cause a stellate configuration in imaging resembling invasive carcinomas. A helping distinguishing feature is the presence of a radiolucent center which favors the diagnosis of a radial scar. The majority of nodular SA are classified as level 4 (suspicious for malignancy) according to the Breast Imaging Reporting and Data System (BIRADS) [22].

Some studies found that ultrasonography, mammography, and MRI have unsatisfactory sensitivity and specificity to differentiate SA associated with breast carcinoma from those SA with no carcinoma. When diffusion–weighted magnetic resonance imaging (DW–MRI) was assessed to find if it can increase ability to differentiate benign from malignant lesions in the breast, it was found that this type of imaging modality is useful for differentiating these two categories of breast lesions [26]. After the recent advances in machine learning tools, radiomics appeared as a rapidly evolving and powerful tool in diagnosis and research. Radiomics identify certain imaging characteristics within lesions or tissues such as shape, size, heterogeneity, topography, etc. This involves the extraction of quantitative, and ideally reproducible, information from diagnostic images, encompassing complex patterns that are challenging for the human eye

to recognize or quantify. This data is sometimes added to demographic, histologic, genomic, or proteomic data to reach certain diagnosis based on machine learning models to be used for clinical problem solving. These radiomic models were applied to differentiate SA from carcinomas and were found useful[27].

An interesting study used machine learning tools to compare the clinical and ultrasonic characteristics of breast sclerosing adenosis and invasive ductal carcinoma. Based on the different features between the two groups, researchers constructed a predictive nomogram for SA. According to the constructed nomogram, SA should be suspected in asymptomatic young women [younger than 36 years of age], who present with small–size lesions [less than 10 mm] with distinct margins, homogeneous internal echo, and lack of blood supply [28].

Molecular basics of the pathogenesis of Sclerosing adenosis

The exact pathogenesis of SA has been poorly understood for decades. Scientists observed that breast cancers which has underlying SA, had a significant increase in frequency of harboring bilateral and multicentric cancers when compared to breast cancer patients without SA [29]. This observation raised a hypothesis that there is a possibility that certain molecular changes are evolving in the SA lesions which will accumulate to evolve into carcinoma one day. After the advances in molecular biology, emerging molecular evidence provided greater understanding of the biology of SA lesions. Degnim AC and colleagues conducted a sophisticated analysis comparing gene expression profiles between SA lesions that progressed to carcinoma within 10 years and those that did not. It was intriguing to discover that SA, which developed cancer, possesses distinct genomic alterations [30]. These alterations are referred to as gene signatures. Identification of this signature indicates that this SA will evolve into carcinoma within 10 years. In spite of such interesting results, the application of these findings in clinical practice is however difficult because the positive predictive value will likely be low. Moreover, when the proliferative capacity of the cells in SA was assessed, it was found that increased proliferation (measured by increased Ki–67 expression) in the SA lesion carries an approximately twofold increased risk for subsequent breast carcinoma as compared to SA lesions with lower proliferation [31].

The molecular changes, not only in the SA eithelail cell component that play an essential role in the pathogenesis of the lesion, but it is also the changes in the myoepithelial cell component too.

Myoepithelial cells of the acini play a key role in maintaining the normal mammary gland function and cellular architecture. There are paracrine interactions between these cells and the luminal epithelial cells. Myoepithelial cells are considered part of the mammary stem cell niche. These cells are important for regulation of cell cycle progression, keeping the normal polarity of the luminal epithelial cells and inhibiting cell migration and invasion outside the basement membrane of the acini. Therefore, myoepithelial cells have been considered the "natural tumor suppressors " of breast. In experimental studies, myoepithelial cells were found to constitutively express high amounts of proteinase inhibitors that include tissue inhibitor of metalloproteinase 1, protease nexin–II, alpha–1 antitrypsin, and maspinin. These are all molecules essential in inhibition of cellular invasion [32]. In SA, myoepithelial cells undergo hyperplasia in addition to other phenotypical changes. When compared with normal breast ducts and lobules, myoepithelial cells in SA showed reduced expression of several protiens and markers that are normally present in the myoepithelial cells [33].

At the chromosomal level, some proliferative breast lesions were found to have chromosomal abnormalities in certain segments. Interstitial deletions of the small arm of chromosome 3 (3p with 3p 12–14) was found the common deleted segment in papilloma and diffuse proliferative breast lesions with atypia [34]. These changes were thought to be early neoplasia–relevant aberrations. However, they do not seem to be sufficient by themselves to unleash a malignant process [34]. No research studies were conducted to examine chromosomal structural abnormalities in SA.

Aneuploidy [A condition in which there are extra or missing chromosomes in some or all the cells in the body] was detected in (11%) of SA lesions that have no associated with malignancy compared with (80%) SA lesions that are associated with carcinomas [35]. Authors concluded that aneuploidy seen in SA may help identify lesions with a higher relative risk of being associated with breast carcinoma and hence that may require more aggressive management than diploid lesions [35]. These reported biological alterations in SA lesions both in the luminal cells and in the myoepithelial cells in addition to the presence of associated carcinomatous lesions demonstrate that essential precursor biomarkers of malignancy are present many years prior to cancer development [30] Identification of those alterations associated with progression to cancer could advance risk prediction for women with SA, and provide insight into driving early events in breast carcinogenesis.

Risk for development of breast carcinoma

Will SA evolve into carcinoma? Will all SA develop carcinoma? After how long? Is it possible to differentiate between SA that will advance to carcinoma and those that will not? Is SA a precancerous lesion? These inquiries have persisted over the SA for decades.

Several studies reported higher incidence in the presence of breast carcinomas in association with SA. This association was reported to vary between 7% and 25% [15, 36]. This rate increases in SA of bigger size [37]. The relative risk for development of breast cancer from a SA was found to be around 2.1 [38]. SA has been proposed as a precancerous lesion for tubular carcinoma due to the similar morphology between both diseases microscopically[39]. However, others do not agree with this view because not all SA will necessarily evolve into carcinoma.

In conclusion, there is no suffecient evidence that SA itself is a precancerous lesion, however it is associated with increased risk for breast carcinoma esecially when associated with atyical epithelial hyperlasia [13].

Management

After histopathological confirmation for the diagnosis of SA which is usually done on a core biopsy, the decision to go for excisional biopsy to remove the SA lesions entirely is debatable. The aim that all agree for is to reduce the number of unnecessary surgical excision for a benign lesion that will not develop a carcinoma. Some suggested to follow up by radiology on interval periods. However, Strachan et described a comprehensive approach for managing SA depending on the presence or absence of cellular atypia. If SA is associated with atypia, then vacuum–assisted biopsy (VAB) is recommended. VAB will provide the multidisciplinary team with a more representative pathology sample to direct management [40].

Conclusion

Sclerosing adenosis of the breast is sometimes one of the challenging areas in diagnosis. Accurate understanding of the biological and the morphological nature of the condition and correlation with radiological findings is mandatory for reaching a correct diagnosis. The underlying molecular change in these lesions is still not fully clear mandating further research in this area. Management of the lesion needs a multidisciplinary team decision depending on if the lesion is alone or is it associated with cellular atypia. In some cases, a follow–up plan is needed in the manner and at the frequency tailored for each woman.

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Conflict of Interest

Authors declare no conflict of interest.

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