Fine-Needle Aspiration Cytology of Sclerosing Adenosis of the Breast

A Retrospective Review of Cytologic Features in Conjunction With Corresponding Histologic Features and Radiologic Findings

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Key Words: Breast; Sclerosing adenosis; Fine-needle aspiration; FNA; Core

Abstract

We retrospectively reviewed 25 fine-needle aspiration cases of sclerosing adenosis of the breast in conjunction with histologic features of the paired core-needle biopsy and radiologic findings. The original cytologic diagnoses were benign (n = 19), focally atypical (n = 3), and suspicious for carcinoma (n = 3). The frequent features, although not specific, were low-to-moderate cellularity, bland epithelial cells that focally formed cohesive groups/tubules or occasionally discohesive clusters or individual cells, and fragments of dense fibrous stroma. Some tubules had an angulated configuration. Myoepithelial cells were present in all cases but were scant or absent in small epithelial groups. These cytologic features closely reflected the histologic appearances (ie, compressed and attenuated tubules and sclerotic stroma), but may cause overinterpretation on cytologic smears, especially when angulated tubules, discohesive or individual epithelial cells, scanty myoepithelial cells, and nuclear atypia are noted concurrently. Familiarity with its cytologic features may prevent false-positive diagnosis. Histologic confirmation is recommended for difficult cases.

Sclerosing adenosis (SA) is a benign proliferative disease of the breast that affects mostly perimenopausal women. Histologically, SA is characterized by compact acini and tubules that are often compressed or attenuated by surrounding sclerotic stroma and may sometimes show considerable distortion of the glandular structures, reminiscent of invasive carcinoma. SA is usually small and noted microscopically; however, it may form a palpable mass as a result of confluence of the affected lobules. The latter is also referred to as an adenosis tumor or nodular SA. Clinically palpable lesions may be poorly delineated and firm.

In most cases, SA is detected on mammography. Reported mammographic and ultrasonographic features of SA include microcalcifications, mass, asymmetrical opacity, and architectural distortion. Microcalcification patterns associated with SA are usually amorphous or pleomorphic punctate clusters and scattered amorphous punctate calcifications. However, reported suspicious heterogeneous calcifications on mammograms in 10% of cases. The contour of the mass may vary from well-defined to irregular or, occasionally, spiculated, and most lesions are hypoechoic.

Despite the recent surge in popularity of core-needle biopsy (CNB) for breast lesions, fine-needle aspiration (FNA) remains a cost-effective, fast, and simple procedure that is often the first diagnostic procedure used in some centers or many developing countries to evaluate indeterminate breast lesions detected on imaging. In previous studies, as well as in our experience, benign sclerotic breast lesions potentially generated diagnostic dilemmas that can lead to false-positive diagnoses on FNA samples. It is important to be aware of the cytologic features and diagnostic challenges of these lesions to minimize misinterpretation and
unnecessary diagnostic procedures or prevent inappropriate management.

To date, little has been published about the cytologic features of SA, most of which has been in the form of case reports or small series.11-13 Cytologic features of SA on smears have been described as highly cellular, with sheets or groups of uniform, bland epithelial cells, some of which had a fingerlike branching pattern, numerous bipolar bare nuclei in the background, and hyalinized stromal fragments. Overall, the benign nature of the lesions seemed readily appreciated on FNA samples.11-13 However, these studies did not specify the proportion of SA component present in the surgical specimens examined. In view of the fact that SA did not specify the proportion of SA component present in the surgical specimens examined. In view of the fact that SA is often associated with other benign breast lesions, such as fibrocystic change or ductal hyperplasia,7 some of the features described might represent those of coexisting non-SA benign lesions.

To identify cytologic features that most likely represent SA, we examined FNA samples of lesions that, based on histologic findings of the corresponding tissue biopsy or resection, were composed exclusively or predominantly of SA. We reviewed the FNA cytologic features in conjunction with the histologic features.

**Materials and Methods**

In our routine practice, tissue sampling of a radiologically indeterminate breast lesion usually started with FNA, performed by a radiologist using a 20- or 21-gauge biopsy needle under ultrasonographic guidance. Two needle passes were usually made for each lesion. Direct smears were air-dried for Diff-Quik staining (Stat Lab, Lewisville, TX) and fixed in modified Carnoy fixative (a 6:1 ratio of 70% ethanol to glacial acetic acid) for Papanicolaou staining. The smears were assessed immediately by an on-site cytopathologist. If the cytologic features at the time of immediate assessment were inconclusive for a definitive diagnosis or appeared to be incompatible with clinical and/or radiologic findings, a CNB procedure was concurrently performed by the same radiologist using an 18-gauge needle under ultrasonographic guidance. In some patients, the CNB procedure was subsequently performed a few weeks after the FNA diagnosis was rendered.

To identify cases for this study, we first retrospectively searched the electronic database in the department of pathology for the surgical pathology cases that had a final diagnosis of SA of the breast rendered at The University of Texas MD Anderson Cancer Center (Houston, TX) between January 2003 and February 2010. We then reviewed the histologic slides and pathology reports of each case. Only the lesions in which SA constituted more than 50% of the epithelial component in the histologic sections were included in this study, whereas lesions with coexisting breast carcinoma (either in situ or invasive carcinoma) were excluded. We then identified the corresponding FNA findings of the same lesions from the same database.

We identified a total of 25 SA lesions from 25 patients who fulfilled the inclusion criteria. Histologic diagnoses of all the 25 lesions were made on CNB (17 cases were sampled concurrently and 8 cases were sampled subsequently); 14 cases (56%) were composed exclusively of SA and 9 (36%) had SA with minor component of ductal hyperplasia or fibrocystic change, 1 (4%) had SA with a small focus (approximately 5%) of atypical ductal hyperplasia, and 1 (4%) had SA with a small focus of atypical lobular hyperplasia. Table II. Subsequent surgical resection was performed in 3 patients, and the diagnoses were consistent with histologic findings of the prior CNB. Clinical and radiologic follow-up data were available for 22 patients (mean follow-up time, 31 months; range, 1 to 82 months) and none of these patients developed a subsequent malignant disease at the biopsy site.

Of the 25 FNA cases, 24 had slides available for cytologic review. We retrospectively and semiquantitatively evaluated each case for the following features: cellularity, epithelial cell arrangement (ie, configuration of cell groups and cohesiveness), apocrine metaplasia, nuclear atypia (defined as nuclear enlargement, crowding, pleomorphism, or distinct nucleoli), myoepithelial cells, fibrous stroma, and microcalcifications. The corresponding histologic findings on the CNB were also reviewed in parallel with the cytologic findings in each patient.

Clinical and radiographic information including mammographic findings, the Breast Imaging Reporting and Data System (BI-RADS) score, and ultrasonographic findings of each patient were also reviewed and recorded. This study was approved by the MD Anderson Institutional Review Board.

**Results**

The patients ranged in age from 40 to 67 years (mean, 50 years), and all were women. A BI-RADS score from the mammogram for the corresponding lesions was available in 15 patients: the score was 0 in 9 patients, 2 in 2 patients, 4 in 2 patients, and 5 in 2 patients (Table 1). Ultrasonographic examination revealed solitary lesions in all patients. The lesion sizes ranged from 0.4 to 1.8 cm (mean, 0.9 cm); 16 (64%) of the 25 lesions were smaller than 1.0 cm. Nineteen (76%) lesions had irregular or ill-defined margins, 16 (64%) were hypoechoic, and 3 (12%) were hypervascular.

The cytologic diagnoses of the 25 lesions included benign lesions (ductal hyperplasia, fibrocystic change, or benign fibroepithelial lesion) in 18 (72%) cases, ductal hyperplasia with focal atypical cell clusters in 3 (12%) cases...
Kundu et al / FNA of Breast Sclerosing Adenosis

Table 1
Clinical, Radiologic, and Pathologic Findings for 25 Patients with SA of the Breast

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age (y)</th>
<th>BI-RADS Score on Mammo.</th>
<th>Size (cm)</th>
<th>Features</th>
<th>Cytologic Diagnosis</th>
<th>Histologic Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>52</td>
<td>0</td>
<td>0.5</td>
<td>Hypoechoic lesion with irregular margin</td>
<td>Fibrocystic change</td>
<td>SA</td>
</tr>
<tr>
<td>2</td>
<td>40</td>
<td>0</td>
<td>0.7</td>
<td>Ill-defined hypoechoic lesion</td>
<td>Fibrocystic change vs. fibroadenoma</td>
<td>SA</td>
</tr>
<tr>
<td>3</td>
<td>44</td>
<td>N/A</td>
<td>1.3</td>
<td>Hypervascular lesion</td>
<td>Benign fibroepithelial lesion</td>
<td>SA</td>
</tr>
<tr>
<td>4</td>
<td>40</td>
<td>0</td>
<td>1.6</td>
<td>Lesion with irregular margin</td>
<td>Suspicious for carcinoma</td>
<td>SA</td>
</tr>
<tr>
<td>5</td>
<td>58</td>
<td>NA</td>
<td>0.6</td>
<td>Hypoechoic lesion with irregular margin</td>
<td>Fibrocystic change</td>
<td>SA</td>
</tr>
<tr>
<td>6</td>
<td>46</td>
<td>2</td>
<td>1.8</td>
<td>Hypoechoic lesion with irregular margin</td>
<td>Benign fibroepithelial lesion</td>
<td>SA</td>
</tr>
<tr>
<td>7</td>
<td>41</td>
<td>0</td>
<td>1.2</td>
<td>Ill-defined hypoechoic lesion</td>
<td>Benign fibroepithelial lesion</td>
<td>SA</td>
</tr>
<tr>
<td>8</td>
<td>67</td>
<td>NA</td>
<td>1.4</td>
<td>Ill-defined hypoechoic lesion</td>
<td>Ductal hyperplasia</td>
<td>SA</td>
</tr>
<tr>
<td>9</td>
<td>51</td>
<td>0</td>
<td>0.5</td>
<td>Ill-defined lesion</td>
<td>Suspicious for carcinoma</td>
<td>SA</td>
</tr>
<tr>
<td>10</td>
<td>51</td>
<td>NA</td>
<td>0.4</td>
<td>Ill-defined hypoechoic lesion</td>
<td>Fibrocystic change</td>
<td>SA</td>
</tr>
<tr>
<td>11</td>
<td>42</td>
<td>0</td>
<td>0.4</td>
<td>Ill-defined hypoechoic lesion</td>
<td>Ductal hyperplasia with focal atypical cell clusters</td>
<td>SA</td>
</tr>
<tr>
<td>12</td>
<td>45</td>
<td>NA</td>
<td>1.3</td>
<td>Well-circumscribed hypoechoic lesion, hypervascular</td>
<td>Ductal hyperplasia</td>
<td>SA</td>
</tr>
<tr>
<td>13</td>
<td>61</td>
<td>NA</td>
<td>0.7</td>
<td>Hypoechoic lesion with indistinct margin, hypervascular</td>
<td>Benign ductal cells</td>
<td>SA</td>
</tr>
<tr>
<td>14</td>
<td>56</td>
<td>0</td>
<td>0.8</td>
<td>Well-circumscribed isoechoic lesion</td>
<td>Suspicious for carcinoma</td>
<td>SA, ductal hyperplasia</td>
</tr>
<tr>
<td>15</td>
<td>63</td>
<td>NA</td>
<td>0.7</td>
<td>Hypoechoic lesion with indistinct margin</td>
<td>Ductal hyperplasia with focal atypical cell clusters</td>
<td>SA, ductal hyperplasia</td>
</tr>
<tr>
<td>16</td>
<td>41</td>
<td>4</td>
<td>1.6</td>
<td>Suspicious irregular lesion</td>
<td>Benign ductal cells</td>
<td>SA, ductal hyperplasia</td>
</tr>
<tr>
<td>17</td>
<td>47</td>
<td>NA</td>
<td>0.9</td>
<td>Ill-defined hypoechoic lesion</td>
<td>Ductal hyperplasia with focal atypical cell clusters</td>
<td>SA, ductal hyperplasia</td>
</tr>
<tr>
<td>18</td>
<td>40</td>
<td>0</td>
<td>0.4</td>
<td>Ill-defined lesion</td>
<td>Ductal hyperplasia</td>
<td>SA, ductal hyperplasia</td>
</tr>
<tr>
<td>19</td>
<td>49</td>
<td>5</td>
<td>0.6</td>
<td>Hypoechoic lesion with irregular margin</td>
<td>Fibrocystic change</td>
<td>SA, ductal hyperplasia</td>
</tr>
<tr>
<td>20</td>
<td>52</td>
<td>2</td>
<td>0.9</td>
<td>Ill-defined hypoechoic lesion</td>
<td>SA vs. tubular adenoma</td>
<td>SA, fibrocystic change</td>
</tr>
<tr>
<td>21</td>
<td>47</td>
<td>NA</td>
<td>1.0</td>
<td>Well-circumscribed hypoechoic lesion</td>
<td>Fibrocystic change</td>
<td>SA, fibrocystic change</td>
</tr>
<tr>
<td>22</td>
<td>59</td>
<td>NA</td>
<td>0.6</td>
<td>Ill-defined lesion</td>
<td>Fibrocystic change</td>
<td>SA, fibrocystic change</td>
</tr>
<tr>
<td>23</td>
<td>51</td>
<td>4</td>
<td>0.7</td>
<td>Well-circumscribed lesion</td>
<td>Benign ductal cells</td>
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<td>53</td>
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<tr>
<td>25</td>
<td>56</td>
<td>0</td>
<td>0.4</td>
<td>Well-circumscribed lesion</td>
<td>Benign ductal cells</td>
<td>SA, atypical lobular hyperplasia</td>
</tr>
</tbody>
</table>

BI-RADS, Breast Imaging Reporting and Data System; NA, not available; SA, sclerosing adenosis.

(cases 11, 15, and 17), and suspicious for carcinoma in 3 (12%) cases (cases 4, 9, and 14). In 1 remaining case (4%), the cytologic diagnosis was a benign lesion with a differential diagnosis of SA and tubular adenoma.

Of the 24 FNA cases in which slides were available for review, the cellularity observed in the smears varied: low cellularity in 8 (33%) cases, moderate in 13 (54%) cases, and high in 3 (13%) cases. Large cohesive epithelial sheets were scant or absent in 19 (79%) cases and were more often seen in lesions that contained coexisting non-SA proliferative lesions found in the corresponding CNB samples. All cases showed varying amounts of small cohesive epithelial groups that had acinar or tubular arrangements. Some tubules had an angulated configuration or pointed ends, and Myoepithelial cells with bipolar bare nuclei were found in all cases, and were readily identified within large epithelial sheets but were more subtle or lacking in small epithelial clusters. In only 3 cases (13%), bipolar bare nuclei were readily identified in the background. Apocrine cells were focally present in 5 (21%) cases. Fragments of dense fibrous stroma, some of which were attached to epithelial groups, were seen in 19 (79%) cases. Microlcalkifications were found in 3 (13%) cases. For the 3 lesions that were considered atypical in smears, the CNB diagnoses were SA with ductal hyperplasia in 2 lesions and pure SA for the other. All 3 lesions that were cytologically considered suspicious for carcinoma were proven to be pure SA in the CNB samples. In retrospective review of these 6 FNA cases, small cohesive cell groups/tubules and discohesive cell clusters/single cells were more apparent, whereas large cohesive cell sheets were less evident, as compared with the other cases. Tubules with an angulated configuration or pointed ends were found in 2 suspicious cases. Mild nuclear atypia including nuclear...
enlargement and overlapping was found in 2 suspicious cases and 2 atypical cases.

Correspondingly, histologic review of the 25 CNB samples revealed that the SA components were characterized by expanded lobules and high number of acini and tubules with underlying myoepithelial cells that were often compressed by dense fibrous stroma. Although some acini and tubules had discernible or dilated lumina, others (especially tubules in the center of the lesion) showed elongated tubular structure with narrow or obliterated lumina, mimicking an infiltrative growth pattern of carcinoma Image 2A, Image 2B, and Image 2C. Nonetheless, the lobular configuration, a feature indicative of a benign nature, was retained in all cases and was best appreciated at low magnification. In 4 cases (cases 1, 2, 4, and 17), the distortion of tubules was so substantial that immunohistochemical stains with smooth muscle actin and p63 were required to highlight the myoepithelial cells surrounding the proliferating glands, thus confirming the benign nature of these lesions. In 14 cases, microcalcifications in the tubules or the adjacent stroma were noted.

**Discussion**

With the advance of imaging techniques in the identification of small breast lesions, SA has been increasingly detected. Similar to the findings reported by others, our study demonstrated a wide spectrum of radiologic appearances of SA that, in some instances, overlapped with those of breast carcinoma. Because radiologic differentiation of SA from malignant lesions is not reliable, pathologic analysis is often required for further evaluation. However, pathologic diagnosis of SA may be challenging, even on histologic grounds. For example, in lesions with distorted proliferation of tubules and acini, the benign nature of the lesion may need to be confirmed under low-power view to appreciate the lobular configuration, and sometimes using immunohistochemical stains that highlight myoepithelial cells. It is conceivable that cytologic diagnosis of SA may be even more difficult because of the intrinsic limitations associated with FNA samples, such as the lack of histologic architecture.

CNB is generally a reliable sampling method for establishing the diagnosis of SA. The strengths of our study were the relatively large number of lesions that were sampled via both FNA and CNB and the fact that SA was the sole or major component of the lesions, as confirmed by histologic examination. In addition, the subsequent surgical resection and clinical/radiologic follow-up further support the benign nature of the lesions. These factors allowed us to evaluate the cytologic features that most likely represent SA.

Although the cytologic features of SA that we observed in this study were similar to those described in previous studies, the frequency and proportion of some features seem different. For example, hypercellularity, sheets of benign ductal epithelial cells, and numerous bipolar bare nuclei were constantly described in previous studies, whereas we often observed low to moderate cellularity, varying amounts of small cohesive cell groups/tubules (occasionally tubules with an angulated configuration or pointed ends), and focally discohesive epithelial clusters/single cells. We did observe bipolar bare nuclei in all cases, but they were infrequently seen in the background and were subtle or absent in the small epithelial groups/tubules and in the discohesive clusters. In keeping with other studies, dense fibrous stroma was also frequently noted in our study. These cytologic features reflect quite closely the compressed and attenuated tubules and sclerotic stroma present in the histologic appearances of SA. The low cellularity of SA is likely a result of the presence of dense hyalinized stroma that can entrap the epithelial cells as well as its usualy smaller size. The larger epithelial cell sheets likely represent the adjacent ordinary ductal hyperplasia and the tubules with dilated lumina in the periphery of SA.

Overall, the common features of SA we found were the presence of cohesive cell groups/tubules in an otherwise benign breast aspirate. Recognition of the benign nature in most cases is straightforward. However, false-positive
Cytologic diagnoses have been previously reported. Jayaram and Gupta\textsuperscript{4} reported a case in which SA was misdiagnosed as invasive lobular carcinoma where the cytologic features included high cellularity and small clusters of monomorphic cells with mild nuclear pleomorphism. In our study, the cytologic features that potentially lead to an overinterpretation included the cohesive epithelial groups/tubules, especially those having an angulated configuration or pointed ends; discohesive cell clusters or individual cells with intact cytoplasm; few or no myoepithelial cells; and nuclear atypia. A false-positive diagnosis may occur when these cytologic features are evident and/or are found concurrently in a case, especially when imaging findings are also considered indeterminate or suspicious.

The important finding in this study is that cohesive epithelial groups or tubules with an angulated configuration or pointed ends can be seen in SA. The main differential diagnosis is low-grade breast carcinoma, such as tubular carcinoma. A number of studies have reported that tubular carcinoma can have a uniform and bland cytologic appearance, numerous cohesive cell groups, and some myoepithelial cells, reminiscent of benign proliferative diseases.\textsuperscript{11,16-18} However, tubular carcinomas are more frequently associated with hypercellularity than is SA.\textsuperscript{15} The abnormal tubules or discohesive cells in tubular carcinoma, compared with those in benign lesions, are more abundant and diffuse, and have a more rigid outline or acutely angled configuration.\textsuperscript{10,17,21} During cytologic evaluation, weight should be given to the impression obtained under low magnification in assessing the proportion of different cellular elements, and judiciously use combined cytologic criteria. In cases in which a definitive distinction cannot be made, a tissue biopsy is recommended.

Although the cytologic features described in our study correlate closely with the histologic appearances of SA,
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the features are nonspecific and, therefore, are not prospectively diagnostic for SA. Tubular adenoma and other benign lesions may show similar cytologic features, at least focally. This notion is further supported by the fact that, in our study, the cytologic diagnoses in most cases were fibrocystic change, ductal epithelial hyperplasia, and benign fibroepithelial lesion, even in those cases in which histologic diagnosis was pure SA. Likewise, Cho and Oh compared the cytologic features of SA with those of fibroadenoma and fibrocystic change and found significant overlap.

In rare cases, SA may be involved by in situ or invasive carcinoma. Each breast lesion should therefore be approached prudently using a multidisciplinary approach. If cytologic features show atypical features beyond what is expected for a benign lesion and/or if radiologic findings are suggestive of malignancy (such as spiculated masses, branching or fine linear calcifications, or calcifications in a segmental or linear distribution), a tissue biopsy or resection should be advised for histologic confirmation.

In conclusion, SA may show clinical, radiologic, and pathologic features that overlap with those of breast carcinoma. Although FNA cytologic examination may not provide a specific diagnosis of SA, awareness of the cytologic features of SA and the diagnostic pitfalls can help prevent misinterpretation. A multidisciplinary approach to the diagnosis and management of SA is recommended. Histologic confirmation may be needed for difficult cases.

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References


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