The term “collagenous spherulosis” (CS) was first introduced by Clement and colleagues in 1987 to describe a peculiar change of the breast. The lesion, usually an incidental microscopic finding involving lobular acini and ductules, consists of intraluminal clusters of eosinophilic spherules typically situated adjacent to or encompassed by other benign proliferative processes. In the intervening decade, a small number of reports have described CS in the breast in association with both benign and malignant processes, especially when it presents as a mass. It is of utmost importance to differentiate benign CS from its malignant mimics in order to avoid unnecessary treatment. We report an unusual case of CS manifesting as a mass in the right breast of a 45-year-old female and discuss the problems of differential diagnosis and histogenesis.

Case Report

A 45-year-old female consulted our outpatient department of general surgery due to a mildly tender and hard right breast mass for about six months. On physical examination, a well-defined hard right breast mass, about 2 cm in diameter, was palpated, located at 10 o’clock position and 7 cm away from the nipple. Past medical history revealed that the patient had undergone total hysterectomy for uterine leiomyoma nine months prior to consultation. Mammography showed a heterogeneous density mass in the outer quadrant with out microcalcification. Under the impression of a benign tumor, a simple excision with a margin less than 1 mm was performed. No evidence of recurrence or metastasis was noted in the subsequent 14 months of follow-up.

Grossly, the tumor was a well-circumscribed but non-encapsulated gray yellow elastic mass, measuring...
ing 3 × 1.7 × 1 cm. On sectioning, the cut surface was homogeneously yellow to white. Microscopically, this mass was composed of multi-focal cellular lobules of variable size, surrounded by a rim of loose fibrous tissue in a fatty background (Fig. 1).

Two types of spaces were seen in variable proportion within each lobule. One type was lumina (L) and the other type was spherule (S). The spherules were most commonly found inside lobules and surrounded by epithelium (S), but occasionally they could be seen directly attached to peri-lobular stroma (arrow). Exceptionally, they could be formed completely in the stroma (arrowhead) (Hematoxylin & Eosin stain ×200).

Fig. 2. Two types of spaces were seen in variable proportion within each lobule. One type was lumina (L) and the other type was spherule (S). The spherules were most commonly found inside lobules and surrounded by epithelium (S), but occasionally they could be seen directly attached to peri-lobular stroma (arrow). Exceptionally, they could be formed completely in the stroma (arrowhead) (Hematoxylin & Eosin stain ×200).

cuboidal epithelium containing eosinophilic intraductal secretion. The other type was a spherule identical to that of the so-called CS described by Clement and colleagues. The spherules were typically discrete but occasionally coalesced, and had fibrillar patterns that varied from loosely arranged to more densely packed (Fig. 2). When the latter predominated in the lobule, the lobule exhibited a cribriform pattern (Fig. 1).

Frequently, the peri-lobular stroma of loose fibrous tissue showed invagination into the lobules. When this took place, the spindle stromal cells gradually decreased while they invaginated, and on the other hand, deposition of extracellular fibrillar eosinophilic material increased and finally formed the spherule (Fig. 3). As a consequence, the spherules were most commonly found inside lobules, surrounded by epithelium, but occasionally, were seen directly attached to peri-lobular stroma. Occasionally, they were formed completely in the stroma (Fig. 2).

Several unremarkable terminal duct-lobular units were observed around this tumor. There was no evidence of other benign or malignant processes that accompanied this lesion.

Detection of mucin secretion by pan-mucin stains including periodic acid-Schiff with diastase (PASD), Alcian’s blue, and mucicarmine stains (for neutral,
slightly acidic, and highly acidic mucosubstances, respectively) and immunohistochemical studies for cytokeratin, smooth muscle actin M851, and S-100 protein were performed. Samples of ACC and C-DCIS were examined using the same technique for comparison and the results are listed in Tables 1 and 2.

Table 1. Pan-mucin stain results

<table>
<thead>
<tr>
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<th>PASD</th>
<th>Alcian’s blue</th>
<th>Mucicarmine</th>
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<tbody>
<tr>
<td>CS lumina</td>
<td>+++</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CS spherule</td>
<td>-</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>ACC lumina</td>
<td>+++</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>ACC spherule</td>
<td>-</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>C-DCIS lumina</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
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CS = collagenous spherulosis; ACC = adenoid cystic carcinoma; C-DCIS = cribriform ductal carcinoma in situ; PASD = periodic acid-Schiff with diastase.

Table 2. Immunohistochemical results

<table>
<thead>
<tr>
<th></th>
<th>CK</th>
<th>Actin M851</th>
<th>S-100</th>
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<tbody>
<tr>
<td>CS luminal epithelum</td>
<td>+++</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CS spherular epithelum</td>
<td>-</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>ACC luminal epithelum</td>
<td>+++</td>
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<tr>
<td>ACC spherular epithelum</td>
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</table>

CS = collagenous spherulosis; ACC = adenoid cystic carcinoma; C-DCIS = cribriform ductal carcinoma in situ; CK = cytokeratin.

Discussion

In the study of Mooney and colleagues, who collected eighty-one cases of CS from the files of the Armed Forces Institute of Pathology during the period 1987-1997, CS was correctly diagnosed in only 15%, while 28% were misdiagnosed as malignant or atypical, such as ACC, C-DCIS, or AIH.2

CS bears similarity to ACC its light microscopic pictures, histochemical and immunohistochemical staining properties (Tables 1 and 2), and ultrastructures.1,2,5,6 Both lesions contain 2 types of spaces, one surrounded by cells showing ductal epithelium and containing basement membrane material and mucopolysaccharides. There are three distinguishing characteristics. First, ACC is distinguished from CS by virtue of its infiltrative process characterized by a desmoplastic stromal reaction. Second, malignant cellular appearances including nuclear irregularity, hyperchromasia, and mitosis are consistently seen in ACC and absent in CS. Finally, the ductal epithelium that is present in the cellular lobules and forms variable-sized ductal lumina in CS is rare or forms only small-sized ductal lumina in ACC.

The cribriform pattern of CS simulates C-DCIS and AIH microscopically. The differential diagnosis of CS from C-DCIS and AIH is based on two observations. First, attenuated myoepithelial cells, rather than ductal epithelial cells of C-DCIS and AIH, form the spherules of CS. Immunohistochemical staining for smooth muscle actin establishes the myoepithelial nature of these cells in CS (Table 2). Second, the material within the spherules of CS consists of densely eosinophilic protein or radiating fibrillar ground substances, and they differ in appearance and histochemical staining (Table 1) from the disorganized mucin found in C-DCIS and AIH.4

Involvement of CS with lobular carcinoma in situ is a well-known phenomenon. The principal differential diagnosis between the two lies in the presence of conventional lobular carcinoma in situ, as characterized by a monomorphous population of loosely cohesive atypical cells that replace the luminal cells of acini and intralobular ductules, causing an large extent of entire terminal duct lobular units. The neoplastic cells possess small round, bland nuclei and pale, scant cytoplasm. In addition, involvement of CS with lobular carcinoma in situ is potentially confused with C-DCIS. Differentiating features between CS and C-DCIS have been discussed earlier. Additionally, the neoplastic cells of lobular carcinoma in situ display a loosely cohesive growth pattern that is more in keeping with the properties of lobular neoplasia than ductal carcinoma.4

There are two theories on the mechanism of spheration for malignancy in CS. The first theory is stromal invagination, based on light microscopic and ultrastructural observations of stromal invagination into cellular lobules.3 The second theory, based on observations of the circumscript of the spherules
and the frequent identification of a compressed myoepithelial cell nucleus surrounding CS, favors the interpretation of spherulosis as the result of extracellular material deposition secreted by proliferative myoepithelium.\textsuperscript{1,2,6} Our observation of the gradual transition from stromal invagination to spherule favors the first theory.

In conclusion, the histopathological features of this tumor represent a benign intra-acinar proliferation of ductal epithelium and myoepithelium (so-called epitheliosis) with extensive spherule formation. No matter which the theory precisely describes the mechanism of spherule formation in CS, the spherules are undoubtedly, as supported by histochemical, immunohistochemical and ultrastructural studies, derived from a progressive accumulation of extracellular material, including mucopolysaccharides and basement membrane material.\textsuperscript{1-3,5-7,9} The most important thing is to keep in mind the possibility of CS when a mass like ACC, C-DCIS, or AIH is encountered in the breast.

References


