Ductal Carcinoma In Situ of the Breast: The Pathological Reason for the Diversity of Its Clinical Imaging

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Summary. The hormone-sensitive epithelial cells within the lobules are the major source of ductal carcinoma in situ (DCIS) of the breast. The neoplastic cells grow, and fill and increase the volume of the spaces bound by the basement membrane until they disrupt them. Even extensive cases of DCIS are unifocal in three dimensions and are usually confined to a single segment of the mammary duct system. The neoplastic cells can proliferate within the spaces that have been altered by benign proliferative diseases such as adenosis and multiple papilloma. The concept of unfolding is the key to understanding the morphology of DCIS as well as benign breast cysts, both of which have larger and fewer structures although they originated in the small blind-ending structures within the lobules. Atypical ductal hyperplasia (ADH) can be understood as minimal low-grade DCIS that incompletely fills the spaces bound by the basement membrane. Although ADH, atypical lobular hyperplasia, and lobular carcinoma in situ (LCIS) carry a general risk for later development of invasive mammary carcinoma, DCIS carries a localized risk. The management of the DCIS should be determined based on pathological evidence including grade, size, and surgical margin status.

Introduction

A clear understanding of the normal and pathological anatomy is essential for a correct interpretation of the clinical imaging of the ductal carcinoma in situ (DCIS). For example, the fact that most DCIS originate in the epithelial cells of the ductules rather than the ducts explains why the spaces filled with noninvasive carcinoma cells always have rounded contours and are clustered close together although they measure several millimeters in size. Anatomy also indicates that the ductules have only one exit. If it is blocked, the elevated pressure in the closed spaces caused by cancerous

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growth and accumulation of necrotic material results in fewer and larger spaces containing cancer cells and central necrosis, a so-called comedo pattern characteristic to DCIS. This report focuses on the anatomical aspects of DCIS and benign breast lesions that are relevant to understanding the diversity of their clinical imaging.

Anatomy of the Breast

The breast consists of 15 to 25 segments, or lobes. Each lobe is based on a branching duct system leading from the collecting ducts via segmental and subsegmental ducts to the lobules.

The intraductal spread of breast carcinoma occur along the duct lobular system of one lobe, with no invasion beyond the basement membrane. According to a three-dimensional reconstruction study using computer technology performed by Ohtake et al. [1], the individual duct system is arranged radially, with the nipple at the center, and shows an irregular branching pattern and a sector-shaped overall distribution.

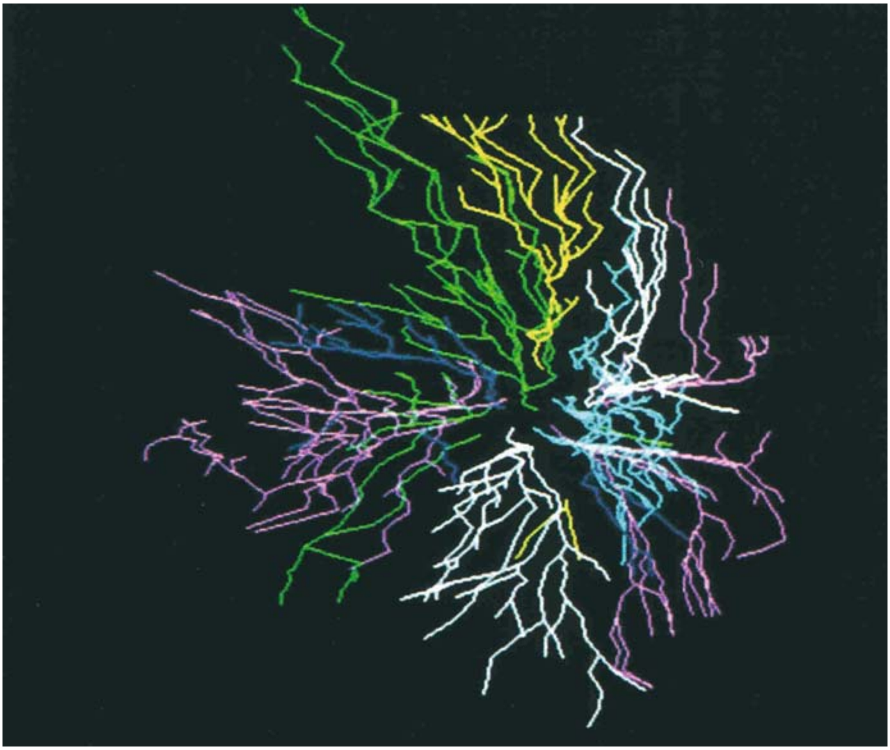

Fig. 1. Complete three-dimensional network model showing all mammary ductal/lobular system (MDLS) individually identified by different colors. This breast specimen included 16 sector-shaped MDLS exhibiting repeated and irregular branching of ducts, here shown skeletally or schematically. (From [1] with permission)

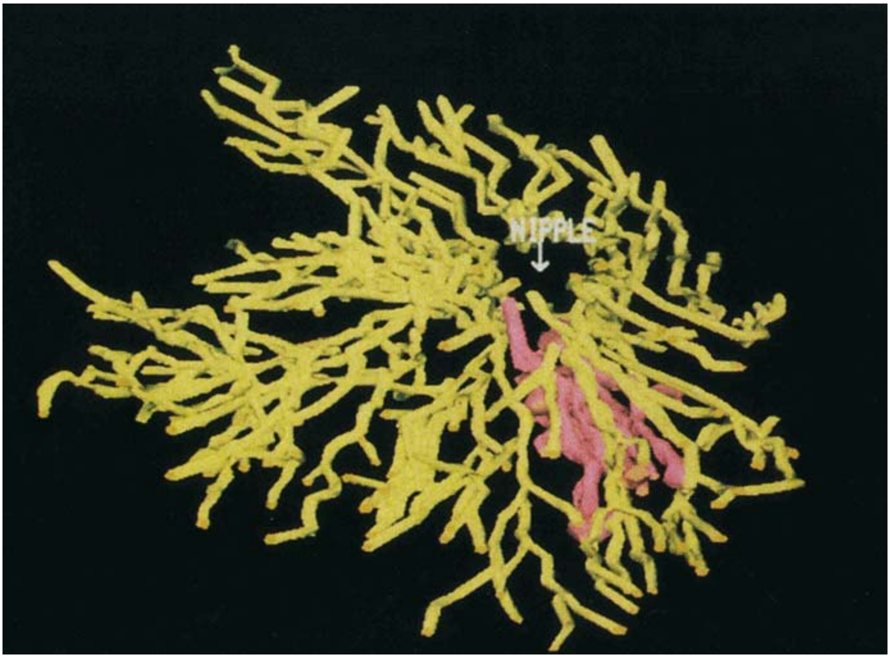

Fig. 2. Complete three-dimensional solid model of the full extent of all mammary ductal/lobular systems (MDLS) in the entire breast. All MDLS are oriented radially, with the nipple at the center (*arrow*). Not a single MDLS is involved by ductal carcinoma (DCIS) (DCIS is shown in *red* and the normal ducts are shown in *yellow*). (From [1], with permission)

Several duct systems overlap one another in the same region of the breast (Figs. 1, 2). Ohtake et al. also noted the presence of intersegmental anastomosing ducts in some of the cases they examined. However, the frequency and the clinical significance of such anastomoses are not known and will need further investigation.

The lobules are functional units for milk production. The terminal ducts give rise to multiple blind-ending branches called ductules or acini. A small portion of the terminal duct together with the ductule (acini) constitutes the lobule. The three-dimensional structure of the lobule is best understood using three-dimensional reconstruction studies, although it is also perceived on aspiration cytology specimens (Fig. 3). A normal lobule measures 0.5 to 8 mm (the average being 1–2 mm).

The breast lobules are the major sources of both benign and malignant breast diseases. Common benign lesions of the breast such as fibroadenoma, cysts, adenosis, epithelial hyperplasia, and multiple papillomas are disorders of the lobules. Furthermore, most breast malignancies also originate in the lobules.

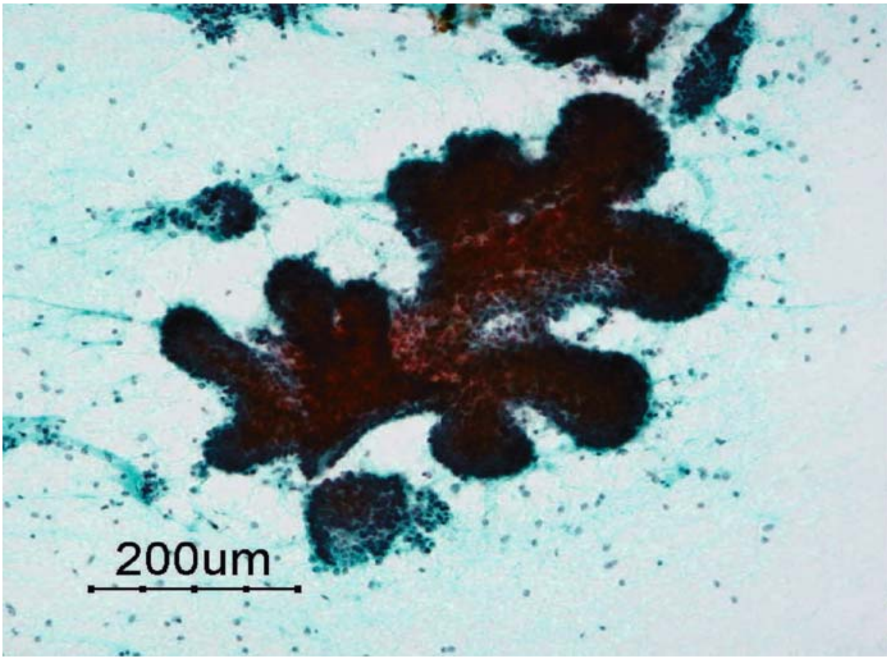

Fig. 3. A breast lobule in aspiration cytology. The three-dimensional structure of the lobule is best understood using three-dimensional reconstruction studies, although it is also perceived on an aspiration cytology specimen

Breast Cysts

The ductule has only one exit. If it is blocked, the increased hydrostatic pressure in the ductules results in a tension cyst. A few larger cysts develop by a “running together” of ductules with concomitant disappearance of the specialized lobular stroma [2]. It is important to note that the cysts can be larger than the dilated ducts in size, although they are derived from the smallest unit of the duct-lobular system. At low magnification, cysts are grouped together and always have rounded contours, demonstrating their lobular origin (Fig. 4).

Fibroadenomas

Polyclonal proliferation of both intralobular epithelial and stromal cells results in fibroadenoma. Therefore, fibroadenoma is also a disorder of the lobule. The relationship between terminal ducts and multiple blind-ending branches (ductules) is well maintained in earlier stages of fibroadenomas, which are refered to as fibroadenomatous nodules or fibroadenomatous hyperplasia. A well-developed fibroadenoma is formed by coalescence of the separate and smaller fibroadenomatous nodules; this means that a fibroadenoma enlarges by central expansion as well as accretion.

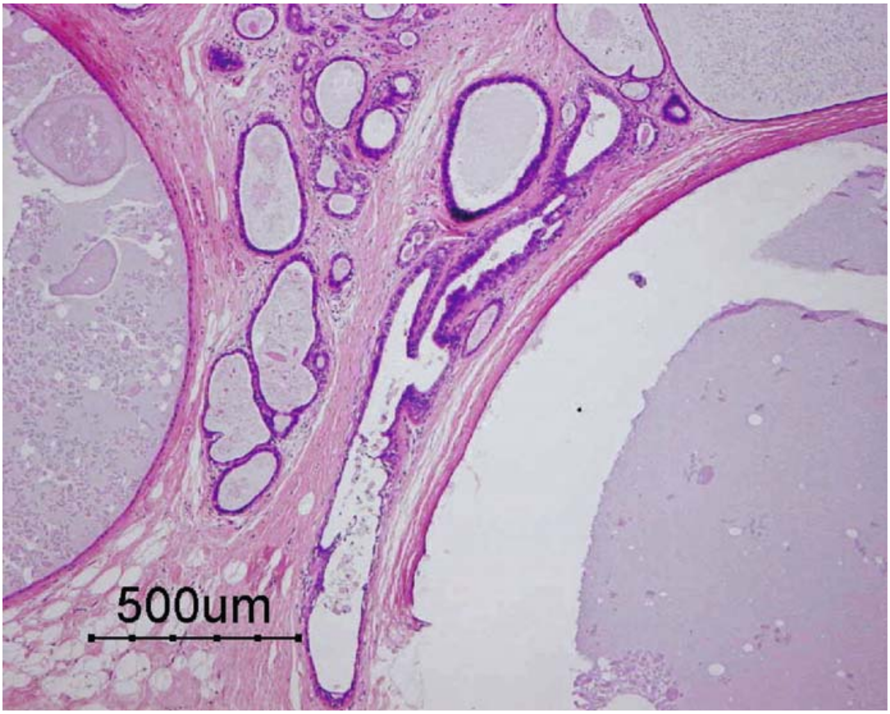

Fig. 4. Breast cysts. At low magnification, cysts are grouped together and always have rounded contours, demonstrating their lobular origin. (Hematoxylin eosin stain)

The process occurs either spontaneously or under hyperestrogenic status; it is arrested at any stage and undergoes hyalinization. Mammographic screening will detect such old fibroadenomas with characteristic coarse calcifications with a popcorn-like appearance.

Adenosis

Adenosis is a proliferation of ductules, resulting in an enlargement of the lobules. Therefore, there is an increase in the number of spaces bound by the basement membrane in adenosis. In sclerosing adenosis, the lesion acquire infiltrative margins. At low-power examination, however, an organoid pattern is recognized. A DCIS may occasionally occur in lobules exhibiting sclerosing adenosis. Such lesions may give a spurious impression of invasion. Recognizing that the space can be altered is the key to understanding the histopathological appearance and the clinical imaging of the DCIS arising in adenosis. In addition to uncomplicated sclerosing adenosis around the lesion, the clue to the correct diagnosis is the retention of lobular architecture. Demonstration of the basement membrane and myoepithelium around the ductules using the imunohistochemical technique is also helpful.

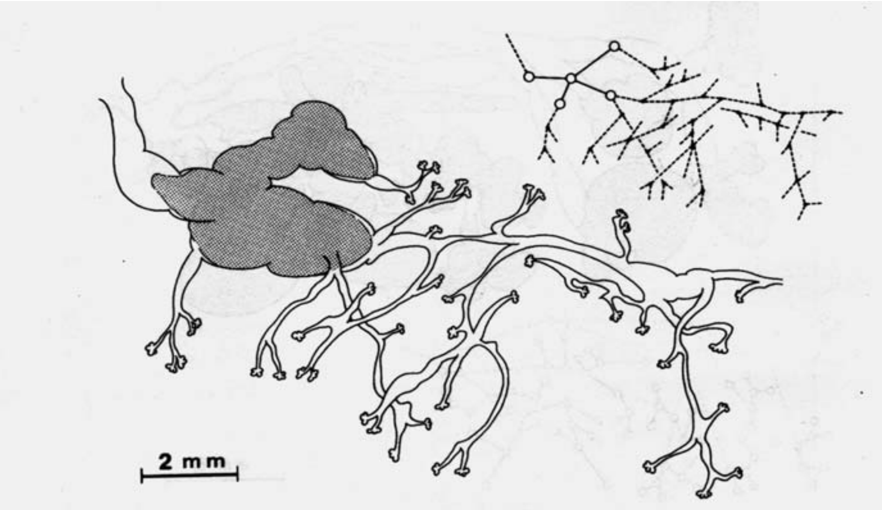

Fig. 5. A solitary papilloma involving only the large ducts. (From [3], with permission)

Papilloma

The term papilloma should be used for villous or arborescent lesions that have a fibrovascular core in the interior of their branches and which are covered by an epithelial layer [2]. In papilloma, the epithelial layer is composed of two cell types, namely, epithelial and myoepithelial cells. The basement membrane exists between the fibrovascular cores and the epithelial and myopithelial cells. Papilloma is occasionally involved by DCIS as well as epithelilal hyperplasia. When the proportion of DCIS relative to the papilloma is small in extent, the diagnosis of atypical papilloma is recommended by some authors.

Sclerosed papilloma is a variant of papilloma complicated by marked sclerosis. Such papilloma often presents a palpable lump, occasionally fixed to the overlying skin. On microscopic examination, the sclerotic areas shows distorted and entrapped epithelial elements, mimicking an invasive carcinoma. For a correct diagnosis, core-needle biopsy and even excisional biopsy may be needed. Some sclerosed papillomas are characterized by an occlusive, adenosis growth pattern surrounded by a fibrotic duct wall. A diagnosis of ductal adenoma is suitable for this variant of sclerosed papilloma.

Conventionally, papillomas are divided into solitary and multiple types. According to a three-dimensional study by Ohuchi et al. [3], solitary papilloma involved only the large ducts (Fig. 5). In contrast, multiple papillomas have their root in the lobule and may spread to the large ducts, suggesting their lobular origin (Fig. 6).

Encysted papillary carcinoma is a special type of DCIS that originates in large ducts. In contrast to the benign papilloma, the epithelial layer of the papillary carcinoma is composed only of neoplastic epithelial cells.

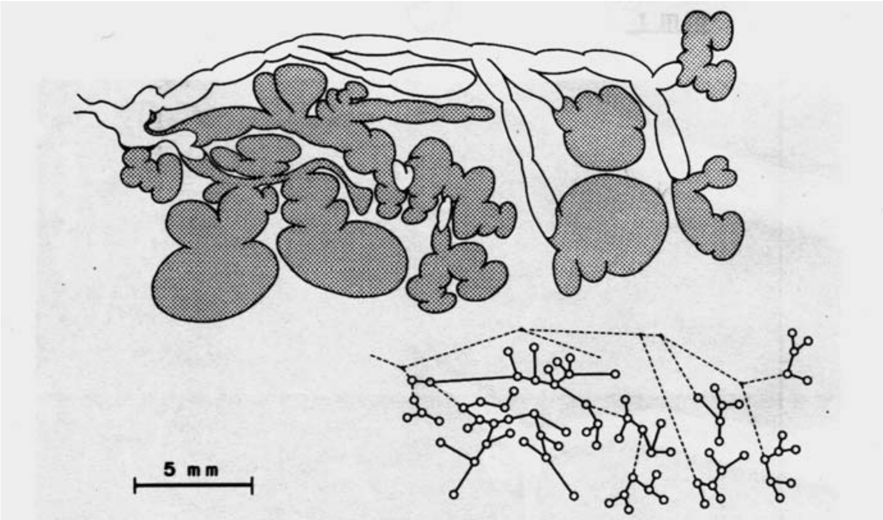

Fig. 6. Multiple papillomas with the roots in the lobule. (From [3], with permission)

Radial Scar

Radial scar consists of ducts and lobules with various amounts of epithelial hyperplasia, adenosis, or ectasia, arranged in a stellate configuration, sometimes indistinguishable from invasive carcinoma on clinical imaging. However, the epithelial elements lack cytological features of malignancy and are surrounded by basement membrane and myoepithelium. DCIS does arise in the spaces bound by the basement membrane in a radial scar. It is difficult to determine whether DCIS arise in the radial scar or preexisting adenosis involved by DCIS takes on a radial scarlike configuration. Demonstration of the basement membrane and myoepithelium around the ductules by imunohistological technique is also helpful.

Epithelial Hyperplasia

Epithelial hyperplasia is an increase in the number of benign cells in the basement membrane-bound spaces. It occurs not only in the spaces bound by the basement membrane in normal breast lobules but also those in benign conditions such as adenosis and papilloma. In mild epithelial hyperplasia, there are three or four cells above the basement membrane. Mild hyperplasia indicates no increased risk for later breast carcinoma. In moderate to severe hyperplasia, the number of cells above the basement membrane is more than four, and this constitutes a mild risk for later breast carcinoma.

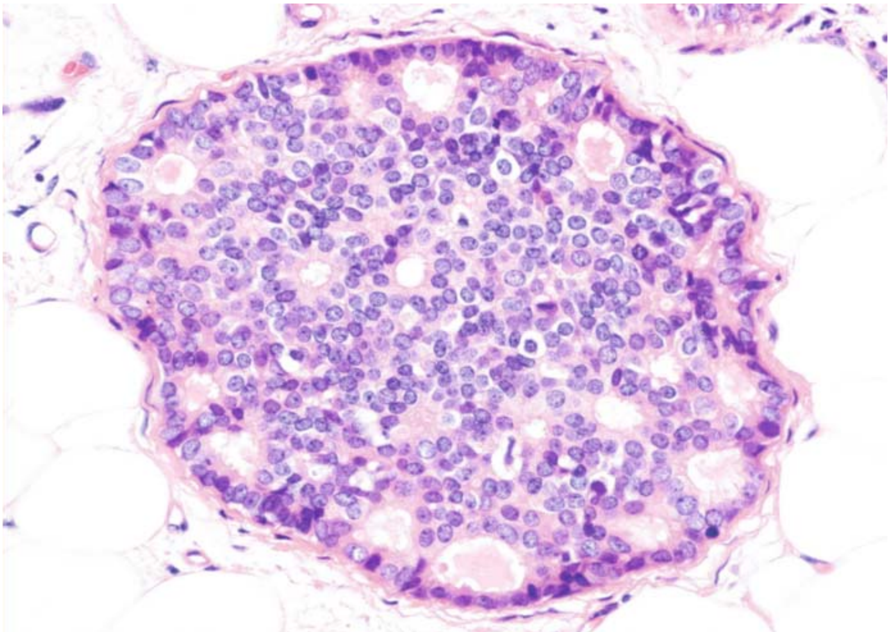

Fig. 7. Atypical ductal hyperplasia (ADH). There is a monotonous cell population resembling low-grade DCIS in the spaces bound by the basement membrane

Atypical Ductal Hyperplasia

The diagnosis of atypical ductal hyperplasia (ADH) requires the presence of a monotonous cell population resembling low-grade DCIS anywhere in the spaces bound by the basement membrane (Fig. 7). However, a major point that distinguishes ADH from low-grade DCIS is that the number of the proliferating cells is limited and the architecture is not fully developed. Lesions of ADH are usually less than 3 mm in size and confined to a lobule. Atypical ductal hyperplasia can be understood as minimal low-grade DCIS that incompletely fills the spaces bound by the basement membrane. Although atypical hyperplasia of ducal and lobular type and lobular carcinoma in situ are believed to carry a general risk for later development of invasive mammary carcinoma, ductal carcinoma in situ is considered to carry a localized risk.

DCIS

The majority of DCIS arise in the hormone-sensitive epithelial cells of the lobule of the mammary duct system. The neoplastic cells grow, then fill and increase the volume of the spaces bound by the basement membrane until they disrupt them. In a case submitted for the three-dimensional reconstruction study by Ohuchi et al. [4], two microscopic foci of DCIS were found, both of them located at the periphery (Fig. 8).

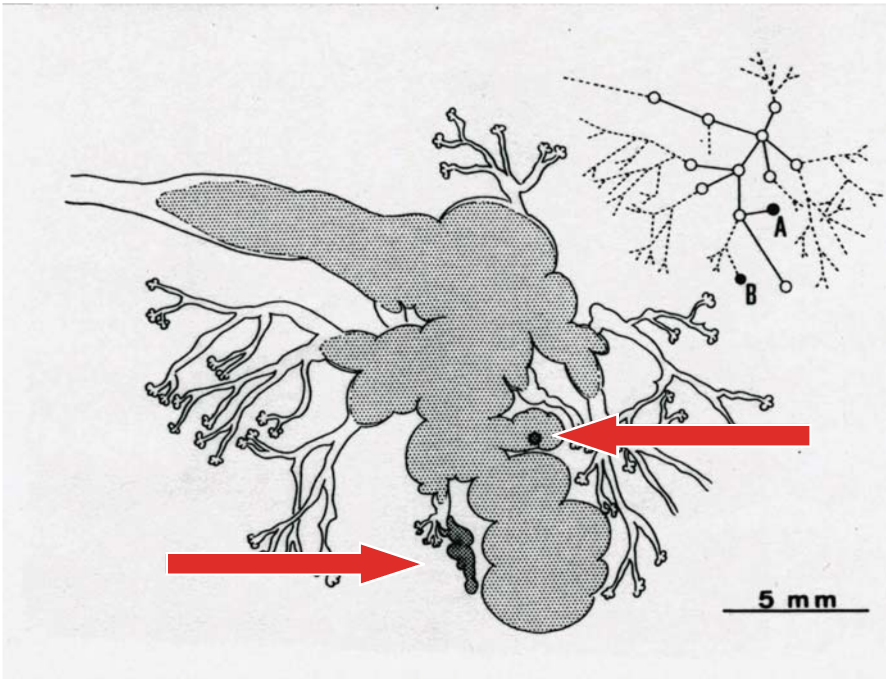

Fig. 8. Two microscopic foci of DCIS are located at the periphery of the mammary duct system. (From [4], with permission)

In another case studied by the same authors, the DCIS is located at the periphery and the papilloma is located in the large duct (Fig. 9). The lobular units distended by cancer cells are often mistaken for cancer of large ducts because of their comparatively large size. The concept of unfolding is essential for understanding the macroscopical appearances of DCIS. With unfolding, a number of small epithelial units merge to give rise to fewer but larger structures.

The origin of most breast carcinomas in the lobule is best appreciated by the study of early cancers at a very low scanning magnification. The spaces bound by the basement membrane are easily distended by increased pressure because they are mostly ductules or terminal ducts that have only one exit. Progressive distension is usually accompanied by unfolding, so that there are only a few, much larger spaces in a diseased lobule. The difference in size between normal and cancerous lobules is striking. The ductule distended and filled by DCIS gives us a false impression of ducts.

Microcalcification is an important diagnostic clue to the presence of DCIS. Microcalcifications characteristic of high-grade DCIS are summarized as follows: these are numerous, have segmental distribution, and exhibit irregularity in density, size, and shape (may be linear or branching). These points are easily understood if one considers that the calcification occurs in the necrotic material in the ductules, terminal ducts, and occasionally large ducts. Although the ductules have rounded contours, the

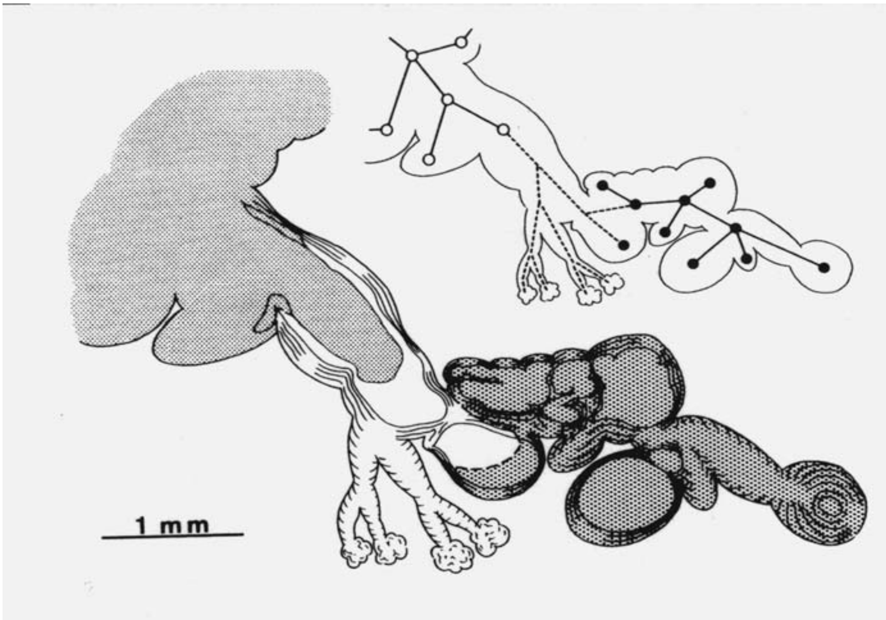

Fig. 9. The DCIS is located at the periphery and the papilloma is located in the large duct. (From [4], with permission)

terminal ducts and large ducts have treelike structures. Therefore, linear or branching calcifications suggest ductal spreading of the carcinoma cells.

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