DCIS histopathology from a historical perspective

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Summary

Ductal carcinoma in situ (DCIS) represents a biologically and morphologically heterogeneous disease. It is characterized by a proliferation of presumably epithelial malignant cells confined within the lumens of the mammary ducts, without evidence of invasion beyond the basement membrane into the adjacent breast stroma. With the widespread use of screening mammography, a dramatic change has occurred in the frequency, management and types of DCIS detected. Historically, there has been some confusion regarding the definition of DCIS and the terminology associated with the histological types of DCIS. In this review, DCIS histopathology from a historical point of view is presented.

Key words: Ductal in situ carcinoma; DCIS.

Introduction

Today, the bond between epithelial proliferative lesions and breast cancer is well established by the majority of pathologists and clinicians specialists on the subject. There is also a general agreement, with minor exceptions, that the proliferative process follows a "continuum" starting from a multilayering of the normal epithelium which progresses to typical hyperplasia and evolves to an atypical one. At this stage, the lesion is considered as precancerous or borderline. The end of this spectrum is when the epithelium undergoes malignant transformation and we are dealing with in situ ductal or lobular carcinoma. The time alloted for these changes is very difficult to be assessed, since during this multistep process unknown factors may stop the "continuum" and the hyperplastic lesions may regress and never undergo malignant transformation [1].

The term ductal carcinoma in situ or intraductal carcinoma (DCIS) describes a heterogeneous group of lesions with a remarkable diversity in radiologic and histologic appearance, as well as in clinical behaviour [2, 3]. DCIS is characterised by a proliferation of presumably malignant epithelial cells confined to the mammary ducts, without evidence of invasion into the surrounding stromal tissue by light microscopic examination. The variety of cytologic appearances of these malignant cells (minimal cytologic atypia to highly anaplastic cytology) and the particularities of growth pattern (non-necrotic micropapillary, papillary or cribriform to solid with central necrosis) comprise a wide spectrum of this disease [4, 5]. Some of these histological features are related to the clinical outcome.

The extent of the disease varies from a highly localized process confined to one or more adjacent terminal ductal-lobular units (TDLUs) to a widespread process that lies from multiple TDLUs to multiple major ducts in one or more segments. The most convincing evidence for this aspect comes from the subgross microdissection studies of Wellings *et al. [*6].

The frequency with which DCIS is detected has increased dramatically. Until 1900, DCIS was a relatively uncommon entity because biopsies were performed for lesions that were palpable and clinically invasive. Due to the advent of mammography, more cases of non-invasive breast cancer are being detected. According to the international literature an incidence of 1-2% of DCIS has been reported in older series [7, 8], while recent studies have shown that 15-20% and in some American series 30-40% of mammographically detected breast malignancies have this type of cancer [9, 10]. Of the 215,000 breast carcinomas diagnosed in the USA in 1999, it is estimated that 39,900 represent DCIS [11, 12].

In the literature data, there has been confusion regarding not only the definition of DCIS but also the terminology associated with the histological types of DCIS [13-37]. This confusion, undoubtedly, has had a significant effect on clinical studies of the disease.

In 1932, Broders defined carcinoma in situ as a lesion composed of malignant epithelial cells that are confined to their natural basement membrane boundaries [13].

...a condition in which malignant epithelial cells and their progeny are found in or near positions occupied by their ancestors before the ancestors underwent malignant transformation.

Three years later, Greenough stated [14]:

The classic and accepted criterion for the diagnosis of cancer of the breast demands that the epithelial cells of the breast gland shall be shown to have infiltrated beyond the basement membrane of the ducts or acini and be identified in the surrounding tissues... It is wise... to regard the anaplastic morphology of single cells or of cells within the normal structural confines, as evidence of hyperplasia, precancerous if you will, but not as justification for the diagnosis of cancer.

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In the breast, carcinoma in situ had been initially linked to intraepithelial carcinoma of the lobules and unfortunately this term did not gain wide acceptance for intraepithelial carcinoma of ducts or intraductal carcinoma. Therefore, clinicians confused the term "intraductal carcinoma" with "duct carcinoma" and the lesion was considered invasive unless it was given a diagnosis of "non-invasive intraductal carcinoma" in the pathology report.

The recognition of DCIS followed the description of in situ lobular carcinoma (LCIS) and it was defined pathologically as early as in 1907. Among the first studies were those of Warren [15]. His observations of "abnormal involution" or "cystic disease" made him hypothesize that carcinoma may develop to duct hyperplasia. He noted, therefore, a type of "adenomatous proliferation" which was worthy of attention.

...under these conditions we most frequently find the combination of abnormal involution and carcinoma. The transition stage is observed when the epithelium no longer confines itself to the cyst cavity, but breaks through the limiting membrane and infiltrates the adjacent structures.

In the mid-1980s some authors used the term DCIS to describe not only lesions confined to the duct system but also tumours that showed areas of invasion. In all editions of Haagensen's book, *Diseases of the Breast,* a lesion was considered DCIS if at least 50% of the carcinoma grew within ducts, meaning that the rest of the tumour (as much as 49%) could be invasive [16-18]. However, about 40% of Haagensen's cases had metastases to the axillary nodes and the 10-year survival was approximately 68-70%. Today, most of the above cases are classified as invasive ductal carcinomas with an extensive intraductal component. McDivitt *et al.* [19] redefined DCIS, excluding any breast cancer with an invasive component and later Rosen *et al.* [20] furthered this concept. In current practice, the use of the terms "intraductal carcinoma" or "ductal carcinoma in situ" is restricted to tumours that in standard histological sections appear confined within the lumens of the ducts and lobules involved in the process. Immunohistochemically, basement membranes in DCIS appear intact or focally discontinuous [21]. A diagnosis of DCIS by itself does not apply to lesions in which there is co-mingling with invasive foci, even if the latter involve a minimal portion of the lesion.

During the early decades of the 20th century, considerable attention was paid to the major structural patterns of DCIS. In 1920, Cheatle [22] referred the term micropapillary carcinoma to describe the lesion, whereas ducts lined by a layer of neoplastic cells giving rise at discontinuous intervals to slender papillary fronds projecting into the ductal lumen. The same term was used by Bloodgood in 1921 [23]. Cheatle referred to the micropapillary element as *laciform* and reported the "cartwheel" appearance of carcinoma in a nearby duct. This type of DCIS has also been described as "clinging" by Azzopardi [24], because the neoplastic epithelium seems to hug the basement membrane. Today, many would describe the "cartweel" appearance as cribriform. In 1941, Muir [25] described the term cribriform and a mixture of micropapillary, papillary and cribriform patterns were seen frequently, especially when DCIS involved multiple ducts.

A multicystic form of DCIS has been described by Rosen and Scott [26], which has been termed cystic hypersecretory intraductal carcinoma. The ducts were distended by densely eosinophilic material resembling thyroid follicles. The authors suggested that a diagnosis of malignancy should be made if an intraductal proliferation of cytologically malignant cells is noted. Today, this type of DCIS is considered as a special subtype of micropapillary carcinoma [27].

In 1934, Bloodgood described the term "comedocarcinoma" indicating the existence of two major patterns: comedo and cribriform [28]. His description is very characteristic:

...I assisted Dr Halstead in exploring a clinically benign tumor of the breast. The patient was 67 years of age and had observed a small tumour for about 11 months... The moment we cut into and pressed on it, there extruded from its surface many grayish-white, granular cylinders, which I called at that time comedos. From the gross appearance the tumour was diagnosed as malignant, and a radical operation was performed.

Two types of comedocarcinoma were recognized by Bloodgood: the "pure comedoadenocarcinoma" and the "comedoadenocarcinoma with areas of fully developed cancer of the breast". The first type had been considered as being entirely intraductal and the second one partly invasive. Subsequently, Bloodgood noted that large tumours with a grossly comedo appearance were falling frequently into the latter category. For these cases he suggested radical mastectomy. His experience from the follow-up of the patients with invasive comedocarcinoma showed that approximately 30% developed metastases and died, but *none of the cases of pure comedoadenocarcinoma was associated with metastases to the axillary nodes; not a single patient died of cancer.* In addition, Bloodgood suggested local excision for small "pure comedo tumours" as the appropriate procedure

...and can be completely excised by cutting through normal breast tissue and closing the wound without injury to the symmetry of the breast.

Later studies demonstrated that some patients who were treated by local excision for comedo carcinomas, developed recurrent carcinoma after one to four years [29]. However in these studies it is not clear if the initial tumours were "pure comedocarcinomas" or had an invasive component as well.

At the same time, Bloodgood mentioned the need for needle aspiration and cytological examination especially for pure comedo tumours, however he did not propose this method to make a distinction between intraductal and invasive carcinoma.

... the tumor had been aspirated before it was explored and from examination of the stained aspirated cells we could only decide that they suggested a malignant tumor. We did not recognize a comedo tumor.

Comedocarcinoma, especially as a pure intraductal

lesion, has not been the subject of many other studies as a separate entity. At this point, two rare alterations of comedocarcinoma need a special citation. The first one is when a marked periductal fibrosis leads to extensive obliteration of the affected ducts. This process was referred to as "healing" by Muir and Aitkenhead [30]. The residual ductal structures are typically round to oval scars consisting of circumferential layers of collagen and elastic tissue. The core representing the center of the duct is often less dense and may contain a few residual carcinoma cells. End-stage scars of periductal mastitis may not be distinguished from those of obliterated comedocarcinoma. Davies [31] studied a large number of breasts and concluded:

...ductal hyperelastosis, obliteration and fibrous plaques are not limited to breasts that are the seat of carcinoma. Indeed the prevalence of these three lesions in major ducts that are unaffected by microscopic changes do not differ significantly in normal and carcinomatous breasts.

On the other hand, one can estimate a severe inflammatory reaction, which is not the result of the immune host response to the tumour and therefore, a mistaken diagnosis of mastitis could be made, due to the fact that the intraductal carcinoma is masked by the inflammation.

Through the years, one problematic area which was presented was the distinction between DCIS with lobular involvement (cancerization of the lobules) and LCIS [32, 33]. Kerner and Lichtig in 1986 [33], described some histological features that favor a diagnosis of DCIS involving lobules over LCIS. These characteristics include: partial involvement of normal size acinar units, residual lumina in involved acini, nuclear pleomorphism, mitotic activity, architectural patterns characteristic of DCIS and foci of necrosis. However, in some cases the above histopathologic features did not permit a clear-cut determination.

Another difficult problem was presented by in situ lesions with areas of central comedo-type necrosis and the typical cytologic features of LCIS. Tavassoli [34] suggested that necrosis rarely occurs in lobular neoplasia and does not necessarily imply a ductal growth pattern. However, Rosen [27] noted that the diagnostic terminology is not universally accepted for such lesions and it is better to categorize them as "examples of duct and lolular carcinoma in situ".

Reently, Tavassoli [35-37] proposed the term "mammary intraepithelial neoplasia, ductal type" or "duct intraepithelial neoplasia" (DIN) for all intraductal proliferative lesions including DCIS as well as intraductal hyperplasia (IDH) and atypical intraductal hyperplasia (AIDH). Based on a classification system, high-grade DCIS with or without necrosis becomes grade 3 DIN (DIN 3), grade 2 DCIS becomes grade 2 DIN (DIN 2), grade 1 DCIS and AIDH are grouped together as DIN1c. Flat epithelial atypia without intraluminal proliferation is designated as DINb, while IDH is designated as DINa. Tavassoli placed all unusual variants of DCIS that lack high-grade nuclear features with or without necrosis into the intermediate category of DIN 2 and specified the subtype (i.e. non-comedo, apocrine, clear cell, spindle cell). More frequently, DIN 2 has been characterised by a micropapillary or cribriform DCIS with mild or moderate nuclear atypia, necrosis or both [37].

DCIS had been a very topical subject in recent years stimulating consensus conferences among pathologists, clinicians and radiologists all over the world. The origin of this interest has been the increased frequency of detection of DCIS resulting from the uptake of mammography since the 1970s. Today, DCIS is the most rapidly growing subgroup in the breast cancer family. Consequently deeper knowledge of the morphology is required, as well as of the biology of the disease. Current approaches to DCIS are based on genetic changes that precede morphologic evidence of the malignant transformation [38] and *medicine must learn how to recognize these genetic changes, exploit them, and, in the future, prevent them* [39].

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