Review

The diagnosis and management of pre-invasive breast disease

Ductal carcinoma *in situ* (DCIS) and atypical ductal hyperplasia (ADH) – current definitions and classification

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Abstract

Intraductal epithelial proliferations of the breast are at present classified into three groups; distinction is made histologically and clinically between usual epithelial hyperplasia and atypical ductal hyperplasia (ADH) and between ADH and ductal carcinoma *in situ* (DCIS). Although evidence indicates that these boundaries are not ideal on a morphological, immunohistochemical, or genetic basis, this three-tier system is accepted and used at present. The current definitions, histological features, and system of classification of ADH and DCIS are described in this manuscript.

Keywords: atypical ductal hyperplasia, ductal carcinoma *in situ*, epithelial proliferation

Introduction

There is a need for an improved classification system for epithelial proliferative lesions and *in situ* malignancy of the breast, as reproducibility of diagnosis and categorisation is problematic. Clearly, classification of any disease process should have biological and clinical relevance as well as high reproducibility. As with diseases elsewhere in the body, distinguishing hyperplasia from neoplasia in the breast is based on identification of a clonal cell process. Clonality is recognised by uniformity of morphology and phenotype, and markers such as cytokeratin expression or hormone receptor expression can be used. While usual epithelial hyperplasia is morphologically and phenotypically heterogeneous, atypical ductal hyperplasia (ADH) and established ductal carcinoma *in situ* (DCIS) are homogeneous in cell type and marker expression. In addition, studies of loss of heterozygosity in low-grade DCIS and ADH have revealed similar genetic changes in the two conditions [1]; this finding is interpreted as confirmatory evidence that these are clonal processes and both therefore fulfil the basic concept of neoplasia. The frequency of loss of heterozygosity in cases of usual hyperplasia is much lower.

The conceptual distinction between benign neoplasia and *in situ* malignancy in the intraductal epithelial proliferations of the breast has been arbitrarily drawn at the boundary between ADH and low-grade DCIS. This may not be the appropriate place. Indeed morphological, immunohistochemical, and genetic studies indicate that it is more appropriate to draw the boundary between usual epithelial hyperplasia and ADH [2]. Nevertheless, this three-tier system is the system accepted and used clinically at present and is outlined below.

Atypical ductal hyperplasia

The distinction between DCIS and ADH is based on evidence derived from many series, including studies by David Page and co-workers [3]. These have been supported by other studies, such as the Nurses' Health Study [4,5]. Clearly, ADH is a rare condition [6], being seen in 4% of symptomatic benign biopsies [7], although it is more common in association with screen-detected benign microcalcifications (31%) and is seen most commonly as an incidental finding [7].

The significance of the diagnosis of ADH lies in the increased risk of invasive breast carcinoma, which is about

ADH = atypical ductal hyperplasia; DCIS = ductal carcinoma *in situ*.

four to five times that of the general population [8–12] and may be even greater for premenopausal women (approaching a sixfold risk) [12]. This risk is further increased if the patient has a first-degree relative with breast cancer (10-fold risk) [8,13,14].

The diagnostic criteria used to define ADH are imperfect. ADH was described initially based on exclusion rather than positive criteria, i.e. the recognition of some but not all of the features of DCIS (as well as the lack of the characteristics of usual-type epithelial hyperplasia) [8]. This definition of ADH has been updated and, while the diagnosis stills rests on an absence of all the features of DCIS, additional supporting features have been described [15,16]. The view of Page and colleagues that the cellular changes of DCIS are present but occupy fewer than two separate duct spaces is widely accepted. Others use a 2-mm cutoff; a lesion less than 2 mm in maximum dimension being classified as ADH and a larger one as DCIS [17]. These criteria recognise essentially the same lesions. In essence, ADH is usually small and focal, measuring less than 2 to 3 mm. Larger foci are accepted if associated with a radial scar/complex sclerosing lesion or a papilloma.

There are three components to the diagnosis of ADH, namely the architectural pattern, cytology, and disease extent. ADH is formed from a uniform population of small or medium-sized, round, cuboidal or polygonal hyperchromatic cells, which are regularly arranged. The nuclei are evenly distributed and may form a rosette-like pattern. Single small nucleoli only are present. Mitoses, particularly abnormal forms, are infrequently seen. Geometric spaces are present and, in the cribriform type, the cells are arranged at right angles to the bridges formed. Micropapillary ADH is also recognised and a solid pattern may very rarely be seen. Small foci of necrosis may rarely be identified in ADH and do not indicate that the process should be classified as DCIS.

At present, it is recommended that the diagnosis of ADH should be restricted to lesions that show the features described by Page and colleagues [8,15], to which the quantified risk of developing breast carcinoma is linked. Even then, the diagnosis of ADH should be made with caution and only if low-grade DCIS has been seriously considered in the differential diagnosis. Lesser changes for which the possible classification lies between florid usual epithelial hyperplasia and ADH are less relevant with regard to a risk of developing breast carcinoma and should not be classified as ADH. However, it should also always be borne in mind that a proliferation at the edge of a biopsy may represent the periphery of a more established lesion of DCIS and further excision of the adjacent tissue may be warranted.

The major problem of ADH is the difficulty in achieving acceptable levels of concordance or consistency in diagnosis. Various strategies have been used to try to improve its recognition, including revision of the criteria, providing a more positive basis for recognition, and education and emphasis on the use of one system by all for diagnosis [15]. Despite the adoption of such principles, the reliable classification around the boundaries of ADH and the 'borderline' epithelial intraductal proliferations in the breast remained elusive in several [18,19], although not all [20], studies.

Ductal carcinoma *in situ*

DCIS is defined as a proliferation of malignant epithelial cells within the breast parenchymal structures with no evidence of invasion across the basement membrane. This lack of invasive foci may be confirmed with immunohistochemical assessment for the presence of myoepithelial cells (e.g. smooth muscle actin, smooth muscle myosin) or basement membrane (collagen type IV, laminin). Pure DCIS accounts for 15 to 20% of breast cancers compared with only 5% of cases before the advent of breast cancer screening [21–23].

DCIS is a unicentric disease process, as shown by elegant three-dimensional studies showing that only one region of the breast is involved in the vast majority of cases and two-thirds of tumours involve only one quadrant [24]. However, the natural history of DCIS is not well understood, as it has largely been extrapolated from historical series and reassessment of previously misdiagnosed lesions, most of which were low grade. The numbers in these series are low; in the series of Page and colleagues [25,26], 28 patients were found to have DCIS from the 11,760 biopsies reviewed, and none of these lesions was of the comedo type. Studies suggest that up to 50% of patients with microscopic foci of DCIS develop invasive carcinoma. The invasive lesion occurs in the same area as the original lesion [27,25], indicating a precursor process. Series of cases in which DCIS was not completely excised have also been reviewed [28], and these indicate that progression to invasion is related to the subtype of DCIS: comedo disease progresses into invasive carcinoma both more often and more rapidly than low-grade DCIS.

Several systems for subdividing DCIS have been described. The traditional classification based on a combination of architectural growth pattern and cytological features provides poor reproducibility, with up to 30% of cases in multicentre trials requiring reclassification [29]. The National Coordinating Group for Breast Screening Pathology in the United Kingdom [16] recommend a system derived from the work of Holland and colleagues [30], classifying DCIS as high, low, or intermediate grade based on cytonuclear features.

High-nuclear-grade DCIS is composed of pleomorphic large cells with abundant, including abnormal, mitoses. Architecture is variable, although often solid. Central

necrotic debris may undergo calcification. Low-nuclear-grade DCIS is composed of uniform cells, which are small. The nuclei are also small, although larger than in adjacent normal epithelium. Low-nuclear-grade DCIS frequently has a cribriform or micropapillary configuration; often both patterns are seen in the same lesion. Individual apoptotic cells or small foci of necrosis may be seen and associated calcification may be present, usually within inspissated secretions. Intermediate-grade disease is diagnosed if the neoplastic nuclei show pleomorphism of a degree between high- and low-grade DCIS. The nuclear-to-cytoplasmic ratio is often high in intermediate disease. The growth pattern may be micropapillary or cribriform but is often solid. Some degree of polarisation around architectural features may be seen.

This system of classification has clinical relevance and shows reasonable reproducibility [31]. Several other systems for typing of DCIS have been proposed, including categorisation based on nuclear grade and necrosis [32,33]. Silverstein and colleagues [32] have grouped DCIS into high-grade, non-high-grade with necrosis, and non-high-grade without necrosis and found an association between the subtypes and local recurrence and disease-free survival [34].

Conclusion

The existing system for the classification of intraductal epithelial proliferations assumes a spectrum from usual epithelial hyperplasia through ADH and low-grade DCIS to high-grade disease. Recently published work using comparative genomic hybridisation to investigate DCIS of the breast has prompted the proposal of a hypothetical model for the pathogenesis of DCIS, which recognises genetic lesions associated with particular morphological subtypes. These data also indicate that ADH/low-grade DCIS is more closely related to lobular *in situ* neoplasia than to high-grade DCIS. Thus new molecular genetic techniques are demonstrating that current dogma is untrue: (a) the fundamental separation of LCIS from DCIS may not be appropriate; (b) distinguishing ADH from low-grade DCIS is illogical; (c) the assumption that DCIS is a spectrum of the same disease is flawed. It is likely that some of these new methods will form the basis of a revised system of classification in the future with an underlying molecular genetic basis while maintaining clinical relevance.

This article is the second in a review series on *The diagnosis and management of pre-invasive breast disease – current challenges, future hopes*, edited by Sunil R Lakhani.

Other articles in the series can be found at http://breast-cancer-research.com/articles/review-series.asp?series=bcr_Thediagnosis

Competing interests

None declared.

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