Cytological and architectural heterogeneity in ductal carcinoma in situ of the breast

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Abstract

Aim—The traditional architecture based classification system of ductal carcinoma in situ (DCIS) has been criticised on the grounds that individual lesions often show more than one pattern resulting in a large mixed category. New DCIS classification systems have emphasised the importance of cytological grade, which is reputed to be more uniformly expressed throughout a lesion. This study investigates the hypothesis that cytological heterogeneity is less common than architectural heterogeneity within DCIS lesions.

Methods—121 cases of DCIS were graded as poorly, intermediately, or well differentiated according to a recently developed classification system that employs cytonuclear morphology as the major diagnostic criterion. Cases were categorised as *pure* when only one grade was present and as *mixed* if more than one grade was observed. Architecturally the cases were classified as solid, cribriform, micropapillary, or papillary and were described as *pure* if only one architectural pattern was present and as *mixed* if more than one pattern was seen. The incidence of cytological heterogeneity was compared with that of architectural heterogeneity. The presence of necrosis was assessed as an independent parameter and the relation to DCIS grade evaluated.

Results—Using the cytology based classification system 102 cases (84%) were classified as pure (65 poorly differentiated, 25 intermediately differentiated, and 12 well differentiated) and 19 cases (16%) as mixed. Extensive necrosis was observed in 61 (50%) cases and was closely correlated to DCIS grade. Architecturally 46 cases (38%) were classified as pure (38 solid, 5 cribriform, 2 micropapillary, and 1 papillary) and 75 (62%) as mixed.

Conclusions—Cytological heterogeneity is much less common than architectural heterogeneity in DCIS lesions. The assessment of cytonuclear morphology is therefore likely to provide more consistent information about DCIS, particularly in small biopsy specimens where only part of the lesion may be available for examination.

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Ductal carcinoma in situ (DCIS), once an uncommon disease, now accounts for up to 13% of all newly diagnosed breast cancers. This largely results from the detection of DCIS by mammography screening. With the increased numbers of cases available for study it has become apparent that DCIS is a heterogeneous condition with differing clinical outcomes,¹⁻¹¹ emphasising the need for a prognostically relevant histological classification system. The traditional system classifies DCIS according to architectural patterns and the presence or absence of luminal necrosis.¹²⁻¹³ Comedo, solid, cribriform, micropapillary, and papillary forms are described. The development of this system has greatly facilitated the recognition of DCIS and its distinction from epitheliosis. This system is disadvantaged by the fact that many cases show more than one architectural pattern resulting in a large mixed category.¹¹⁻¹⁴ Apart from comedo DCIS, which appears to be a more aggressive lesion, architectural patterns are not predictive of biological behaviour. In the past few years a number of alternative classification systems have been proposed.^{4-8, 11, 14-17} In general these have emphasised the importance of cytonuclear features, which appear to be more closely related to clinical outcome and biological characteristics. Proponents of the new classification systems also suggest that cytonuclear morphology is more constant throughout a lesion than architectural pattern. This is of obvious importance as decisions regarding patient management are currently based on the assessment of biopsy specimens where the entire lesion may not be available for examination. Using the system described by Holland *et al*¹⁵ that employs cytonuclear morphology as the key diagnostic criterion we graded 121 cases of DCIS into one or more categories and compared the degree of heterogeneity with that observed when the cases were classified using the traditional architecture based system.

Materials and methods

The study population comprised 121 patients with DCIS, 26 of whom also had early invasive carcinoma (microinvasion or invasion up to 5 mm). All patients were diagnosed and treated at the General Infirmary at Leeds between 1984 and 1994. Cases were identified using the SNOMED Diagnostic Retrieval System. Age at presentation ranged from 29 to 88 years (median 55). Sixty six patients (55%) were symptomatic and in 55 (45%) DCIS was detected mammographically. Seventy nine patients (65%) underwent mastectomy and 42

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(35%) had local excision. All histological sections from each case were reviewed in detail.

DCIS was graded as poorly, intermediately, or well differentiated according to the method

Figure 1 Poorly differentiated DCIS showing a solid growth pattern and luminal necrosis. The nuclei are markedly pleomorphic and there is no cell polarisation.

Figure 2 Intermediately differentiated DCIS showing a cribriform growth pattern. There is some nuclear pleomorphism but this is less marked than that seen in poorly differentiated DCIS. Cell polarisation is evident focally around intercellular spaces.

Figure 3 Well differentiated DCIS showing micropapillary and cribriform growth patterns. The nuclei are uniform and there is good polarisation with orientation of the cells towards the duct lumen.

of Holland *et al.*¹⁵ This system categorises DCIS into three groups based on nuclear morphology and, to a lesser extent, on cell polarisation. Poorly differentiated DCIS (fig 1) comprises cells containing large, pleomorphic nuclei with no tendency to cell polarisation. Central necrosis is a frequent but not invariable finding. In intermediately differentiated DCIS (fig 2) the nuclei are less pleomorphic and cell polarisation is present focally. Well differentiated DCIS (fig 3) comprises small cells with monomorphic nuclei and prominent polarisation of cells. Cases were described as pure when only one grade was present and as mixed when more than one grade was observed.

Architecturally DCIS was classified as solid, cribriform, micropapillary, or papillary. Because of the lack of uniform agreement as to what constitutes comedo,^{8 18} we did not use this as an architectural category. Cases in which the cells surrounding an area of central necrosis showed a solid growth pattern were classified as solid. Cases were described as pure when only one architectural pattern was present and as mixed when more than one pattern was seen. Necrosis was assessed as an independent parameter and was scored as absent, focal, or extensive.

Each case was graded by two observers and any discrepancies resolved by consultation at the double-headed microscope. The incidence of cytological heterogeneity was compared with that of architectural heterogeneity. The relation between the presence of necrosis and DCIS grade was also evaluated.

Results

Cytological heterogeneity was much less common than architectural heterogeneity in individual DCIS lesions (fig 4). One hundred and two cases (84%) showed a single DCIS grade; 65 poorly differentiated, 25 intermediately differentiated, and 12 well differentiated. The remaining 19 cases (16%) showed mixed grades, 16 of which included areas of poorly differentiated DCIS. In contrast a pure architectural pattern was observed in only 46 cases (38%); 38 solid, 5 cribriform, 2 micropapillary, and 1 papillary. Mixed architectural patterns were identified in the remaining 75 cases (62%); two patterns in 60 and three patterns in 15. Necrosis was present in 99 cases (82%) and was extensive in 61 (50%). Extensive necrosis was documented in 28 of 46 cases with a pure architecture, in 33 of 75 with a mixed architecture, and was observed in association with solid, cribriform, and micropapillary growth patterns. Fifty eight of the 61 lesions showing extensive necrosis were graded as poorly differentiated and three as intermediately differentiated. The presence of extensive necrosis was significantly related to DCIS grade ($\chi^2 = 32.14$, $p < 0.0001$).

Discussion

The cytology based classification system used in this study was developed by a group of European pathologists in response to the need for a clinically relevant method for classifying DCIS.¹⁵ This system has been validated by

Figure 4 DCIS classified according to a cytology based system (A) and the traditional architecture based system (B). The percentage of cases showing mixed architectural patterns is much greater than that showing a mixture of cytological grades.

comparison with oncogene and cell proliferation markers, which have been shown to be related to prognosis in invasive breast carcinoma.¹⁹ In addition a close correlation has been demonstrated between DCIS differentiation and the histological grade of the invasive component in tumours composed of in situ and invasive ductal carcinoma.²⁰ This suggests that the grade of the invasive carcinoma developing from DCIS can be predicted from study of the DCIS component alone. Although this DCIS classification system has not yet been evaluated prospectively or retrospectively the results of these correlative studies suggest that the system is likely to be clinically predictive. Morphologically, nuclear grade is the major diagnostic criterion but the system also takes account of architectural differentiation by assessing cell polarisation. In this respect this classification system is more in keeping with the modern approach to the classification of invasive lesions than other cytology based DCIS classification systems. It also differs from other cytology based classification systems in not relying on comedo necrosis as a diagnostic criterion.

In this study we have demonstrated that lesional heterogeneity is much less common when DCIS is classified using a cytology based classification system instead of the traditional architectural approach. Mixed grade was documented in 16% compared with mixed architectural patterns in 62% of the 121 cases studied. In cases where a mixture of grades was observed only two grades were identified in any one case. Apart from a single case in which separate areas of well and poorly differentiated DCIS were identified, the remaining mixed cases showed a combination of well and intermediately differentiated DCIS or intermediately and poorly differentiated DCIS.

Architectural heterogeneity in DCIS has been assessed by others with reported incidences of up to 61% as in our study.^{11 14 21} Using nuclear grade and the traditional architecture based system in a study of 112 cases of mammographically detected DCIS, Harrison *et al* recently reported cytological heterogeneity in 16% and architectural heterogeneity in 61% of cases, almost identical results to those detailed in this study.²¹ They also reported a similar incidence of necrosis, the presence of

which was closely associated with high grade DCIS. This similarity of results reinforces the view that cytological characteristics are more constant than architectural patterns in DCIS. It also suggests that DCIS classification systems that rely primarily on the evaluation of nuclear morphology are reproducible in different centres.

DCIS lesions featuring prominent luminal necrosis were traditionally designated comedo, and a broad subdivision of DCIS into comedo and non-comedo categories has been proposed. There is, however, little agreement about what precisely constitutes comedo. Definitions include the presence of extensive necrosis, central necrosis surrounded by a proliferation of cells showing a solid growth pattern, and central necrosis in association with high nuclear grade. This study has demonstrated a significant correlation between the presence of extensive necrosis and poor DCIS differentiation. This is in keeping with the results of other studies reporting a strong correlation between the presence of necrosis and high nuclear grade,¹⁸ and the development of invasive carcinoma following previous excision of DCIS.^{1 8 22} However, in our study, necrosis was not identified in all cases classified as poorly differentiated by cytological criteria, supporting the views of others that the categorisation of DCIS by necrosis only is over simplistic.

The natural history of DCIS is still unfolding. The introduction of mammography screening means that many of these lesions are now being detected and surgically removed at an early stage in their evolution. Histopathologists are increasingly diagnosing low grade DCIS that in the past may not have been recognised. Similarly, heightened awareness of the potential of DCIS to recur, sometimes as an invasive lesion, has led surgeons to ensure complete excision with a rim of normal tissue. In order to make any meaningful comparison between data from different centres it is essential that pathologists employ a classification system that is reproducible and generates defined categories that can be related to prognostic indicators and ultimately to clinical outcome. The finding in this study that cytological characteristics are much more constant than architectural patterns in DCIS suggests that the assessment of cytonuclear morphology is likely to generate more accurate information about an individual lesion. This is obviously important in cases where only part of the lesion is available for examination. The low incidence of cytological heterogeneity results in a smaller mixed category and cases can be categorised according to the worst grade. This is less easy to apply to an architecture based classification system where it is not clear which pattern is likely to dictate the potential biological behaviour of the lesion.

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