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Combined Histologic and Cytologic Criteria for the Diagnosis of Mammary Atypical Ductal Hyperplasia

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Over the last decade we have been involved in evaluating lesions in the breast between recognizable malignancy and certain benignancy. This is an approach that imposes a borderline between the two categories of benign and malignant and challenges the long-held dichotomous posture of "cancer yes" or "cancer no" as the two exclusive categories. We believe that some of our presentations of this phenomenon in both its practical and philosophical aspects[1-3] may have been less than clear, and this presentation is to clarify and focus on those aspects we have found to be most effective in fostering understanding. These criteria have not changed since 1982,[2,4] but their original presentations did not emphasize the necessity of using three different sets of criteria: cytologic features, histologic pattern, and anatomic extent of lesion.

This presentation will involve the criteria for diagnosing atypical ductal hyperplasia (ADH); the criteria are specifically defined and have been verified recently in a large prospective study.[5] The practice of disease classification and nosology has been an integral part of clinical medicine for millennia. Identifying a constellation of related clinical findings is almost always the basic step that precedes a more fundamental understanding of the disease process under scrutiny. Often, the discovery begins with a series of successive approximations (refinement of definitions, addition of data points, etc) in the direction of absolute truth. A vital concomitant is the linkage of prognostic data with disease outcome for which the disease must have precise and reproducible criteria of diagnosis. Moreover, the criteria must be tested in diverse settings to allow independent verification of prognostic findings. Precision of definition and reproducibility of prognostic findings are prerequisite to the acceptance of the criteria's utility and their widespread adoption.

It is our feeling that although the great majority of diagnoses in surgical pathology have been reproducible, recent trends have focused attention on the border zones between categories. This has increased the necessity for heightened precision in surgical pathology definitions and criteria. The criteria we have presented previously for atypical hyperplasia in the breast have been tested in multiple centers and have gained wide acceptance. One reason for the general acceptance has been that the definition, together with the prognostic links, has confirmed most observers' intuitive opinion. Accepting the usefulness of intermediate lesions (ADH and atypical lobular hyperplasia)[2,6] between that which is recognizable as cancer and that which is not ought to have some prognostic impact given that (1) there are a myriad of different morphologic lesions at the microscopic level in the breast, (2) a few have long been recognized as "malignant," (3) most have been considered as "benign," and (4) some imperfectly suggest ductal carcinoma in situ (DCIS) and have been called imprecisely "benign" or "malignant" while our practice was in the dichotomous "cancer yes" versus "cancer no" mode of diagnosis.

Paradoxically, however, that intuitive approach also may have been the basis for questioning the concept and/or reproducibility of the definition of atypical hyperplasia.[7] Reproducibility can be expected to break down when intuitive concepts are not tethered to precise criteria of definition. We have no quarrel with those who do not wish to use the information presented here; their negative posture, by the same token, does not detract from the utility and predictability of the definitions.[8,9]

In the area of morphology of mammary proliferative lesions we have found that it has been the general practice for surgical pathologists to emphasize the use of either cytologic or histologic pattern criteria. In the context of discussion of features defining ADH, some senior surgical pathologists have responded with comments such as "I can diagnose them on low power and don't need to look at high power" (thus not using cytology) and others have said "I make the differential [as to whether there is atypia] on the basis of cytologic criteria."

Our approach to mammary proliferative lesions recognizes three categories of criteria: cytologic features, histologic patterns, and semiquantitative extent of change. If there is some disagreement among observers, the recognition that these three related but not synonymous categories need to be evaluated brings a great deal of precision to analyses and, thus, fosters agreement among observers. While there is considerable

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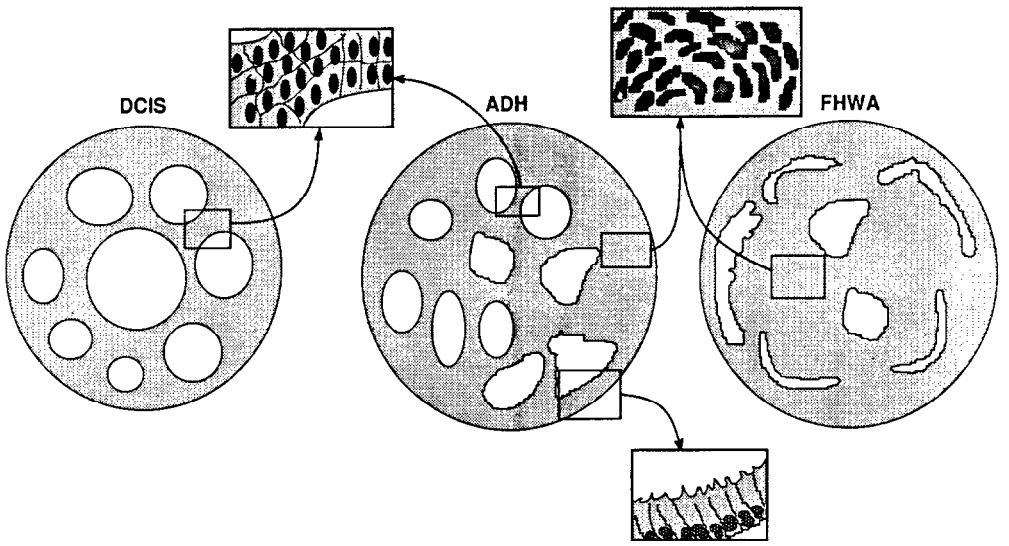

FIGURE 1. Ductal carcinoma in situ versus ADH versus florid hyperplasia without atypia: cytology and histology. Ductal carcinoma in situ (DCIS) features smooth, punched-out luminal borders within involved, basement membrane-bound space. The cytologic features are regular and present throughout the entire population of at least two basement membrane-bound spaces. Florid hyperplasia without atypia (FHWA) is the most densely cellular and extensive of the proliferative disease without atypia lesions, also called "papillomatosis." There are ragged, often slit-like luminal borders. The nuclei throughout the involved area show the variability and tendency to a swirling pattern, as illustrated. Atypical ductal hyperplasia (ADH) has features predominantly of the noncomedo, cribriform DCIS, but also some features of proliferative disease without atypia or normally polarized cells within the same basement membrane-bound space.

congruence between pattern and cytologic findings, the low power pattern does not always predict cytology in these proliferative lesions. The minimal requirement involves a population of uniform, neoplastic-appearing cells.

GUIDELINES FOR EVALUATION OF PROLIFERATIVE DUCTAL PATTERN LESIONS

Many of these lesions involve lobular units, but they are not of the "lobular" series of lesions recognized by atypical lobular hyperplasia and lobular carcinoma in situ, and are distinguished by cytologic and histologic patterns.[10]

1. Florid hyperplasia without atypia exhibits swirling (streaming) patterns of cells. Intercellular borders are usually ill defined. There is irregularity of nuclear shape, chromasia, and position, and there are irregular, often ragged, serpiginous slit-like secondary spaces, most marked centrally.
2. Ductal carcinoma in situ, noncomedo type has a population of evenly spaced, uniform cells with uniformly oval to rounded nuclear features, comprising without doubt the entire population of cells throughout two membrane-bound spaces (a measure of the extent of the lesion). Cytoplasm is usually pale and intercellular borders are usually distinct. Secondary spaces have smooth, rounded "punched-out" borders (cribriform architecture) and rigid, nontapering bars can be found. The approach of Tavassoli and Norris[11] addresses this borderline between ADH and DCIS, noncomedo type with an overall size criterion that is a useful adjunct.
3. Atypical ductal hyperplasia exhibits partial involvement of the basement membrane-bound space by a cell population of the type defined above for DCIS, noncomedo type. Usually, the second (nonatypical) cell population consists of columnar, polarized cells of the type usually seen in the ductal lamina positions immediately above the basement membrane (Fig 1).
4. Upper limit of ADH. When in doubt (between ADH and DCIS), the more benign diagnosis is appropriate (ADH).
5. Lower limit of ADH (ADH *v* no atypical hyperplasia).
   a. To qualify for ADH (as opposed to florid hyperplasia without atypia), the bothersome cell population usually, but not always, has uniformly hyperchromatic nuclei.
   b. To qualify for ADH (as opposed to florid hyperplasia without atypia), the bothersome cells need to comprise an entire nontapering bar crossing a space or at least comprise a cell population of six or seven cells across. This guideline emphasizes the need for a population of similarly appearing "neoplastic" cells.

   NOTE: Each upper and lower limit borderline has its own set of criteria, ie, between proliferative disease without atypia versus ADH and ADH versus DCIS. One practical outcome of all this is that a lesion recognized to be intermediate between proliferative disease without

atypia and DCIS (ie, ADH) is almost without exception a tiny lesion of less than 3 mm in largest size. There is no absolute or solitary division between "cancer yes" and "cancer no."

In conclusion, one fact is without dispute: if diagnosticians agree not to agree on criteria, they will disagree. It is the criteria of ADH linked with the underlying biologic derivations and reproducible consequences that recognizes the increased risk of cancer, not the words or the "experts" applying them.

Historically, we have proceeded from a learning set of approximately 1,000 cases[3] to a test set of many more in which criteria were compared with clinical outcome.[2,6] The criteria for ADH were altered in the test set because in the 1978 study[4] no separation of cancer risk between atypical hyperplasia and ordinary hyperplasia was found in the ductal series. Basically, a conscious effort was made to exclude the complex and more solid examples of florid hyperplasia and recognize as ADH only those cases with features of DCIS. Several confirming studies have been done recently.[11-14] Other biologic and molecular measures of these lesions have been ascertained.[15,16] However, it seems clear that a combination of histologic pattern plus cytologic features is quite precise[17] and has been linked repeatedly to predictive ability with regard to breast cancer risk.

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