Lobulocentricity of Breast Hypersecretory Hyperplasia With Cytologic Atypia

Infrequent Association With Carcinoma In Situ

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Key Words: Hypersecretory hyperplasia; Atypical ductal hyperplasia; Ductal carcinoma in situ; Enlarged lobular units; Cytologic atypia

Abstract

Intracytoplasmic and extracytoplasmic features of secretion, similar to lactational changes, occasionally are seen in the nonparous human breast, usually are lobulocentric, and often have aberrant cytologic and nuclear changes. In these “hypersecretory hyperplasias” (HHs; 38 women) there is bubbly cytoplasm with irregular apical cytoplasmic and/or nuclear protrusions. In a review of 138 HH cases the following additional associated changes were found: nuclear atypia (HHA, 22 women), atypical ductal hyperplasia (ADH-HH, 24 women), and ductal carcinoma in situ (DCIS-HH, 54 women). A diagnosis of DCIS-HH requires involvement of true duct(s) and of several contiguous lobular units, emphasizing the importance of extent and overall size and similar cytology and histologic arrangement of intercellular spaces indicating a homogeneous cell population. Cases of HH regularly are characterized as having adjacent and nearby lobular units with quite diverse cytologic patterns. The major impact of this study is to recognize that HHA may be regarded as having uncertain significance when found alone in the usual presentation in a single unit, but that formally defined ADH and/or DCIS may be locally present.

Enlarged lobular units with various cytologic changes present a challenge in breast pathology. These are generically atypical, usually because of the cytologic characteristics, and often have columnar shape. The few articles addressing this problem have emphasized cytology1-3 (columnar alteration with prominent snouts and secretions [CAPSS]) or the prominent lobular units with varied cytologic and hyperplastic changes.4 A review of relevant articles since the 1960s indicates that understanding of clinical relevance has been stilted by the use of different names for similar changes. We believe that these enlarged lobular units with columnar (and other cytologic) alterations (ELUCAs) are a favored, although uncommon, site for the development of formally identified atypical hyperplasia usually of a “ductal” pattern.4-6

Cytologic atypia only, when confined to lobular units, lacks proven clinical relevance even with marked nuclear enlargement and hyperchromasia that often are present in these hypersecretory lesions. We believe that the current clear increase in these lobulocentric “atypias” is related to the increased sensitivity of mammography and the identification of secretory calcified material as discerned from the usual, more dense calcifications. This article addresses a range of changes in these prominent and enlarged lobular units with secretory and hypersecretory changes.7

Similar lesions were first described by Rosen and Scott8 and Guerry et al.9 Although the article by Guerry and colleagues accepted an atypical hyperplasia category apart from the designation of ductal carcinoma in situ (DCIS), clear guidelines for segregation were not presented.7 We assessed, in this study, standard criteria for atypical hyperplasia10 (ductal and lobular patterns) and DCIS5,11-13 occurring in the backdrop of these hypersecretory and, usually, lobulocentric lesions.
Materials and Methods

Excisional biopsy specimens including mastectomy specimens from our consultation files recorded as hypersecretory were reviewed. These cases were selected from approximately 7,300 biopsy and excision specimens submitted for consultation during 1996 and 1997. Core needle specimens were excluded. There were 376 cases included in this cohort, and standard glass, H&E-stained slides retained from 187 cases were reviewed. The study was limited to cases of enlarged lobular units (3-8 mm) with expanded acini associated with intraluminal secretions and cytoplasmic changes of vacuolization. We excluded cases described as hypersecretory when the changes were primarily those associated with examples of lactational units, apocrine adenosis, and microcystic lobules with flattened epithelium, leaving a total of 138 cases with adequate material for review and multiple lobular units involved by hypersecretory hyperplasia (HH) with or without associated changes of hyperplasia, atypical ductal hyperplasia (ADH), or DCIS. Also, cases of so-called cystic HH without evident lobulocentricity and resemblance to thyroid parenchyma were excluded, noting these are rare. Atypical lobular hyperplasia associated with hypersecretory changes also was recorded.

Extent was defined as the greatest distance or extent of lesions on available slides. We could not estimate 3-dimensional extent directly because we studied cases sent in consultation and lacked the full information of gross extent available from fresh samples. However, histologic slides of entirely submitted tissue could be reviewed for all but 12 cases, and the original surgical pathology reports were examined. Therefore, the extent was considered evaluable in all cases. Ductal involvement meant the presence of lesions in extralobular but not intralobular ducts. Cases of HH with coexistent invasive mammary carcinoma were included in the analysis, although few such cases had been submitted for consultation.

Histologic Findings

To qualify for HH, the cells were characterized by bubbly cytoplasm with irregular apical cytoplasmic and nuclear protrusions and by intracytoplasmic and extracellular secretions and an increase in cell numbers. These hypersecretory and hyperplastic changes were requisite findings for inclusion in the study. We segregated the lesions into 4 categories for HH and associated lesions: (1) HH without atypia (HH), (2) HH with nuclear atypia (HHA), (3) atypical ductal hyperplasia (ADH) with HH (ADH-HH), and (4) DCIS with HH (DCIS-HH). There is no sharp distinction between categories 1 and 2 that include relatively minor variations from usual, as well as marked, cytologic atypia. Categories 3 and 4 include specific diagnostic criteria as cited.

The nuclei of epithelial cells with HH often are large in the solitary lactational unit. These changes may be regarded as analogous to the hypersecretory changes seen in the endometrium. The changes, usually referred to eponymously as Arias-Stella changes, also show protruded, pleomorphic, hyperchromatic nuclei and vacuolated clear cytoplasm. The irregular apical cytoplasmic and nuclear protrusions often were lacking in the micropapillary patterns of ADH and DCIS. Pattern and extent of uniform cellular population are the criteria for the differential diagnosis between HHA and ADH-HH and also between HHA and DCIS-HH. HH occasionally shows mounds and short papillae of hypersecretory cells.
sitting on a layer of normal epithelium Image 2. This pattern represents the mildest form of hyperplasia and cytologic atypia seen in these hypersecretory lesions.

HHAs were characterized by proliferation (more than 3 cell layers) with nuclear atypia, loss of polarity, and no specific features of ADH or DCIS. When specific features of ADH (which have been linked to clinically demonstrated increased breast cancer risk) or DCIS are recognized, a diagnosis of ADH or DCIS is made based on the following criteria: DCIS, noncomedo type, has a population of evenly spaced, uniform cells throughout 2 membrane-bound spaces, almost always more than 3 mm in greatest extent, and involving at least 2 lobular units and extralobular ducts. Some of the other spaces may be involved partially. The “basement membrane–bound space” is a phrase used to be inclusive of the determinant glandular and ductal structures of the breast (acini, ductules, terminal ductules, and ducts). These are the primary epithelial structures in the human breast. Secondary spaces are luminal-like, intercellular spaces formed within these primary spaces when hyperplastic lesions (defined by more than 2 cells above the basement membrane) are not solid, but rather have hollowed intercellular areas. These are recognized in usual-pattern hyperplasia as being largely slit-like rather than round. Secondary spaces in DCIS have smooth, rounded, punched-out borders (cribriform architecture) or are characterized by rigid, nontapering micropapillae in which regular placement of cells is seen (micropapillary architecture).

ADH has features of noncomedo, low-grade DCIS, but also some features of proliferative disease without atypia, specifically with normally polarized cells within the same basement membrane–bound space. The neoplastic cells defining ADH are not present throughout an entire involved space but often constitute at least 50% of the cell population within the space. The cellular arches and spaces between them are crisply and clearly punched out as seen in DCIS but clearly limited in extent. Generally there is an absence of architectural distortion of involved lobular units other than enlargement. Usually the overall size of a lobular unit is less than 3 mm in a single focus but can be more than 3 mm if the foci of ADH are noncontiguous or partially involving enlarged lobular units, as in ELUCA. Such atypical cribriform and solid proliferations of monomorphous cells meeting defined criteria with involvement of multiple lobular units and with extension to major adjacent ducts nearly always satisfy criteria for DCIS.

Image 2, Image 3, Image 4, Image 5, Image 6, and Image 7 demonstrate typical HH, HHA, ADH-HH, and DCIS-HH.

Results

The median age of patients in each category assessed was approximately 50 years Table 1.

The defining hypersecretory features were regularly present in similar patterns throughout individual and somewhat enlarged lobular units, often 2 to 5 mm in largest diameter, and never larger than 8 mm. Large lobules (>80 acini in a lobule, which usually are seen in young women) were found in about 25% of each category. Calcification in secretion was present in about 80% of cases. In addition to lobular-based involvement, only ADH (3 [13%] of 24 ADH-HH) and DCIS (54

Image 2 A and B. Hypersecretory hyperplasia with nuclear atypia has increased cellularity and nuclear enlargement. Note that most of the enlarged nuclei appear similar and have a relatively inapparent or smudged chromatin pattern. Calcification of the secretory material is evident (A, upper right) (A, H&E, ×300; B, H&E, ×400).
[100%] of DCIS-HH showed ductal involvement (Table 1). The number of ducts involved was 1 or less for cases of ADH-HH. When ductal involvement was present, it was solitary and did not involve the entire duct circumference. Extralobular ducts were involved only rarely in ADH-HH but were the defining feature of DCIS-HH. The extent or overall size of HH, HHA, ADH-HH, and DCIS-HH averaged 12.0 mm, 11.6 mm, 6.5 mm, and 17.7 mm, respectively. A micropapillary pattern was dominant in 40 (91%) of 44 cases of DCIS-HH and in 18 (82%) of 22 cases of ADH-HH. The extent of micropapillary pattern of DCIS-HH and ADH-HH averaged 17.6 mm and 6.9 mm, respectively.

Multiple foci (2-6 foci) of ADH-HH (representing 25% [6/24] of total cases) were identified. Several separate lesions interspersed among normal lobules in a slide were identified in about 19% (11/59) of HHA and HH cases. In contrast, in DCIS-HH, no multiplicity was identified with only the single diagnostic focus of DCIS present in continuity (without interspersed normal lobules). Associated histopathologic findings also were present [Table 2].

The average age of the 9 patients with infiltrating mammary carcinoma (IMC) associated with hypersecretory hyperplasia was 43.5 years. The average size of the IMC was 8.1 mm and ranged from 1 mm, which consisted of several tubules, through 15 mm. The IMCs associated with hypersecretory changes were predominantly tubular carcinoma, and the infiltrating carcinoma did not show typical hypersecretory changes.

Discussion

We assessed validated criteria for ADH and DCIS in association with hypersecretory lesions. The irregular apical cytoplasmic and nuclear protrusions often were lacking in the micropapillary patterns of ADH and DCIS. Pattern is the most important criterion for differential diagnosis between HHA and ADH-HH and also between HHA and DCIS-HH. HH occasionally shows mounds and short papillae of hypersecretory cells sitting on a layer of normal epithelium (Image 2). This pattern represents the mildest form seen in these hypersecretory changes.

CAPSS1 is somewhat similar to hypersecretory lesions, but apical snouts are the main features in CAPSS.2,3 Our hypersecretory changes are analogous to exaggerated lactational changes. We excluded the lesions with apical snouts and no bubbly cytoplasm or loss of polarity. These cytologic features may coexist in enlarged and prominent lobular units that we have termed ELUCA, as noted by Schnitt.3

The size or extent criterion8,13 can be applied to foci having classic criteria of ADH or DCIS.5,13,17 If there is involvement of adjacent large ducts, even with more irregular micropapillary patterns, we seriously consider diagnosing DCIS most of the time (Table 1) and certainly if the lesions are much more than 3 mm, involving lobular units and at least 1 true duct. Of course, it is necessary to check whether the duct is involved in continuity and whether the lesion is confined in a papilloma. It is interesting that Goldstein and O’Malley18...
Image 51 A, The low-power view demonstrates the really massive enlargement of lobular units, particularly compared with a normal lobular unit at lower right. Patterns of cells with arches in hyperchromatic clumps in the central enlarged spaces define atypical ductal hyperplasia (ADH) in this case (B and C). Micropapillary patterns (C) are also accepted as ADH if limited in extent (A-C) (A, H&E, ×100; B, H&E, ×250; C, H&E, ×300).

Image 61 A, The low-power view shows an enlarged lobular unit with micropapillary fronds adjacent to a terminal duct exiting at upper right of the photograph. These micropapillary fronds in a duct are highly suggestive of micropapillary ductal carcinoma in situ, which is diagnosed if this is more extensive than in 1 or 2 isolated foci (A and B) (A, H&E, ×100; B, H&E, ×250).
described small ectatic ducts lined by atypical ductal cells with apocrine snouts as a lesion associated with tubular carcinoma. The lesion is likely to be lobular involvement of atypical cells rather than cancerization of lobules, particularly if separated from a pattern of DCIS. There is no indication that individual or clustered lobular units without formal criteria of ADH or DCIS even with advanced nuclear atypia have any meaning other than favored association with ADH or DCIS.2,4,5 A practical reason for this conclusion may well reside in the fact that lobular units are normally monoclonal because of the Lyon hypothesis, suggesting that anatomic changes confined to them may have little importance.19,20 Thus, such focal changes are likely local variations in response to hormonal cues.

Patients with HH are distributed over a wide age range. The average age of patients with DCIS-HH was younger than that of patients with HH. Moreover, invasive carcinoma with HH occurred in younger patients (average, 43.5 years) than did DCIS-HH. HH may have a different meaning in younger patients. Of 9 IMCs in this HH setting, 8 tubular carcinomas or variants were noted (Table 2). Rosen21 also reported that CAPSS is associated with lobular carcinoma and tubular carcinoma. Certainly this association in a series of cases chosen for formal consultation demands further study to ascertain whether any favored types of invasive carcinoma are associated with HH. Although we do not know the direct relationship between them, we should be careful to examine specimens with HH for regionally associated carcinomas and formally recognized atypical lesions. Any precise measure of the association of HH with formal atypias and carcinomas (in situ and invasive) will await better-defined cohorts than are available from the selected cases sent for consultation such as this study represents. Most of our cases with associated invasive carcinoma are of low grade and special type (Table 2). Shin and Rosen22 recently describe 9 cases of pregnancy-associated hyperplasia with coexistent DCIS and 1 case with invasive carcinoma also. As with our cases, the denominator and incidence information is unavailable.

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<th>Table 1</th>
<th>Hypersecretory Changes and Features</th>
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<tr>
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<td>HH (n = 38)</td>
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<tr>
<td>Mean age (range), y</td>
<td>52.2 (38-69)</td>
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<tr>
<td>No. (%) of cases with ductal involvement</td>
<td>0 (0)</td>
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<tr>
<td>Extent (range), mm*</td>
<td>12.0 (2-29)</td>
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ADH, atypical ductal hyperplasia; DCIS, ductal carcinoma in situ; HH, hypersecretory hyperplasia; HHA, hypersecretory hyperplasia with atypia. * For the ADH-HH group, the extent is given for 22 cases and for the DCIS group, 44 cases. The numbers of cases were decreased because of insufficient slides to estimate the extent.

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<th>Table 2</th>
<th>Hypersecretory Hyperplasia (HH) and Coexisting Lesions</th>
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<tr>
<td></td>
<td>HH (n = 38)</td>
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<tr>
<td>ADH</td>
<td>5</td>
</tr>
<tr>
<td>ALH/LCIS</td>
<td>0</td>
</tr>
<tr>
<td>IMC</td>
<td>4 (tubular carcinoma)</td>
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<td>Total</td>
<td>9</td>
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ADH, atypical ductal hyperplasia (classic type of ADH, not in the hypersecretory lobules); ALH, atypical lobular hyperplasia; DCIS, ductal carcinoma in situ; HH, hypersecretory hyperplasia; HHA, hypersecretory hyperplasia with atypia; IMC, infiltrating mammary carcinoma; LCIS, lobular carcinoma in situ.
Conclusions

The hypersecretory lesions of the breast are lobulocentric. ADH-HH usually appears focally in one or several hypersecretory lobules. DCIS-HH requires ductal involvement and involvement of several contiguous lobular units and is regularly unicentric. HH with minor degrees of hyperplasia and advanced nuclear atypia may be regarded as having uncertain significance when discovered without formally defined atypical patterns of hyperplasia. However, HH in the breast apparently has a favored association with ADH and DCIS.

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References