The Breast Journal

SHORT COMMUNICATION

Columnar Cell Change With Atypia (Flat Epithelial Atypia) on Breast Core Biopsy—Outcomes Following Open Excision

Magdalena A. Biggar, MBChB, FRACS,*,‡ Kris M. Kerr, MBBS, FRCPA,† Lisa M. Erzetich, MBBS, FASBP,* and Ian C. Bennett, MBBS, FRACS, FACS*

*Wesley Breast Clinic, Wesley Hospital, Brisbane, Queensland, Australia; †Sullivan and Nicolaides Pathology, Brisbane, Queensland, Australia; ‡Middlemore Hospital, Counties Manukau District Health, Auckland, New Zealand

■ **Abstract:** Columnar cell change with atypia (CCCA) is a relatively recently recognized pathologic breast entity considered to be a risk factor for subsequent development of breast carcinoma. The aim of this study was to investigate the significance of finding CCCA on breast core biopsy, by establishing the frequency of other breast pathology on subsequently performed surgical excision specimens. All cases with CCCA as the most advanced lesion on core biopsy were reviewed. After excision, another advanced proliferative lesion was identified in 17 (33%) patients, including three patients (6%) with in situ or invasive carcinoma. An additional five patients (10%) were concurrently diagnosed with primary breast carcinoma at other sites. These findings indicate that when CCCA is found on core biopsy, open surgical biopsy of the relevant area should be performed and that workup of both breasts should be undertaken to exclude coexistent breast carcinoma at alternative sites. ■

Key Words: breast cancer, columnar cell change, ductal intraepithelial neoplasia, flat epithelial atypia, precancerous lesions

Columnar cell change with atypia (CCCA) has been identified as a histologic alteration which may be associated with more advanced breast pathology, including in situ and invasive carcinoma of the breast, and may be a precursor thereof (1). CCCA is being increasingly recognized as a pathologic alteration of the breast, often associated with mammographically suspicious microcalcification, in the modern era of breast screening. It is characterized by enlarged terminal duct lobular units in which the epithelial cells are composed of one to several layers of cuboidal to columnar epithelial cells that show low-grade cytologic atypia. The characteristic changes are predominately cytologic rather than architectural (1,2). Originally described as "clinging carcinoma in situ," other nomenclature includes "flat epithelial atypia," "ductal intraepithelial neoplasia-1a (DIN-1a)" and "columnar alteration with prominent apical snouts and secretions with atypia" (1,2). These lesions have been reported to be present as the most advanced finding ("pure CCCA") in up to 3.7% of core biopsies (3–5), however, there remains uncertainty regarding the management of this lesion when encountered.

The significance of CCCA lies in previously reported associations with other proliferative lesions, including malignancy, in approximately one third of cases. Although there have recently been several publications regarding surgical excision outcomes following the finding of this entity in core biopsy samples, numbers in the subgroups of patients with this finding alone ("pure CCCA") to date are scant (6–8). Our study assessed the final pathologic results of surgical excision specimens, which had been performed as a consequence of detecting "pure CCCA" on core biopsy, to investigate the frequency of finding other breast pathology.

MATERIALS AND METHODS

A retrospective review was undertaken of records from a prospective data base at the Wesley Breast Clinic, the largest private breast facility in South East

Address correspondence and reprint requests to: Ian Bennett, MBBS, FRACS, FACS, 101 Wickham Terrace, Brisbane, Qld 4000, Australia, e-mail: iancben@bigpond.com.

DOI: 10.1111/tbj.12039

© 2012 Wiley Periodicals, Inc., 1075-122X/12

Queensland, which offers screening and diagnostic services to more than 24,000 patients per annum, encompassing records from 2006 to 2010. Suspicious calcifications or mass lesions are subjected to radiologically guided standard core biopsy (14–18 gauge) or vacuum-assisted core biopsy (8–11 gauge), depending on the preference of the breast physician and radiologist involved. The finding of CCCA on biopsy routinely results in a referral to a breast surgeon for formal open excision of the region.

Cases with biopsies containing CCCA as the most advanced lesion ("pure CCCA") were analyzed. Thus, core biopsy specimens containing another high-risk lesion (such as atypical ductal hyperplasia (ADH), atypical lobular hyperplasia (ALH), ductal or lobular carcinoma in situ (DCIS/LCIS) or invasive carcinoma) were excluded. Cases which contained columnar cell change without atypia were also excluded. Data were collected with respect to patient demographics, mode of presentation, risk factors for malignancy, and outcome of subsequent excisions and any concurrent investigations.

RESULTS

Seventy-two core biopsies were found to contain CCCA, however, 21 of these were excluded due to the coexistence of another lesion on the same core sample. Therefore, 51 cases with CCCA as the most advanced lesion ("pure" CCCA) were identified.

The 51 patients involved were women, with a mean age of 50 years (range 29–80), 22 (43%) of whom were premenopausal. Four patients (8%) had a significant family history of breast cancer. Only one patient had a personal history of a previous breast malignancy. All patients underwent mammographic and ultrasonographic investigation in addition to their image-guided biopsy. Only one of the index biopsies was taken in a symptomatic area, in a patient presenting with a breast lump. In 22 (43%) patients, a breast biopsy was performed following asymptomatic screening. In the remainder, presentation with an unrelated symptom (such as breast pain or distant lump) led to an incidental finding on imaging, which required biopsy. Fourteen patients concurrently underwent additional biopsies (i.e., in addition to the "index biopsy" which yielded the "pure CCCA") at another unrelated ("distant") breast location in either the ipsilateral or contralateral breast, as investigation of a separate concurrently identified abnormality. None of these distant concurrent biopsies were taken from the same quadrant as the index biopsy.

Suspicious calcification on mammography was the most common indication for the index biopsy, occurring in 35 patients (69%). In 13 patients (25%), the finding of a hypoechoic sonographic lesion led to the biopsy. In the remainder, an indeterminate mammographic density or sonographic lesion was the finding. The size of the index lesion was generally small: the mean size was 8 mm (range 1–50 mm) on mammography and 10 mm (range 4.8–20 mm) by sonography. Most commonly (22 patients, 43%) the index biopsy was taken from the upper outer quadrant of the breast. The abnormality was unifocal in the majority (44 patients, 86%). A total of 19 patients (37%) underwent a vacuum-assisted core biopsy whereas the remainder had a standard core biopsy.

All patients proceeded to a formal open excision biopsy of the region from which the index core biopsy containing CCCA was taken. Results of the final pathology after excision are presented in Table 1. CCCA remained as the only risk lesion in the index area of breast in 24 patients (47%) after excision. However, another proliferative lesion was identified in 17 (33%) patients: three patients (6%) were diagnosed with malignancy and in 14 patients (27%) other lesions including ADH, ALH, and LCIS were identified. There were no trends between excision findings and correlation with patient ages, risk factors for malignancy, the indication for the index biopsy or the performance of vacuum-assisted cores.

In addition, five (10%) other patients were concurrently diagnosed with primary breast carcinoma at alternative breast sites, unrelated to that of the index biopsy (i.e., a concurrently performed breast biopsy at a different location). Four patients had invasive ductal carcinoma in the contralateral breast, three of whom were symptomatic with a mass. One patient with CCCA on core biopsy from the upper outer quadrant was also found to have ductal carcinoma in the lower inner quadrant of the same breast.

Thus, in this series of 51 patients with "pure CCCA" on breast core biopsy, malignancy was found on open surgical biopsy either in the region of the index core biopsy or at a different distant breast site in a total of eight patients (16%).

DISCUSSION

This series represents the second largest known published report of "pure CCCA" on breast core biopsy correlated with formal open excision and the

Table 1. Most Advanced Pathologic Finding, Following Open Excision Biopsy of the Area From Which a Core Biopsy of CCCA Was Taken. Patients who were concurrently diagnosed with neoplasia at a distant site are indicated by an asterisk (*)

Pathology	Number of patients (%)	Mean age (years)	Mammographic calcifications as reasons for index biopsy (%)	Sonographic lesion as reasons for index biopsy (%)
Malignant				
Invasive ductal carcinoma	1 (2)	46	1 (100)	
Intracystic papillary carcinoma and DCIS	1 (2)	65	1 (100)	
DCIS	1 (2)	36	1 (100)	
Other high risk lesions				
ADH	5** (10)	63.2	5 (80)	1 (20)
ALH	6* (12)	55.8	4 (67)	2 (33)
LCIS	3 (6)	58.3	3 (100)	
CCCA only	24* (47)	50.6	17 (71)	7 (29)
Benign				
Columnar cell change (no atypia)	5* (10)	52.4	2 (40)	2 (40)
Other benign findings	5 (10)	46.8	3 (60)	2 (40)

first to highlight instances of coexistent breast cancer at a distant site. When CCCA was identified as the only abnormality on core biopsy in 51 patients, subsequent excision demonstrated either in situ or invasive ductal carcinoma in three patients (6%) and another advanced lesion such as ADH, ALH, or LCIS in a further 14 patients (27%). In addition, simultaneous primary breast cancer at an alternative site was diagnosed in five patients (10%).

There is currently continued debate as to whether CCCA is a risk factor for premalignant change or is itself a precursor lesion for breast neoplasia. Evidence does, however, exist to support the latter notion, via a well differentiated pathway: Cytologic alterations are similar to that observed in low-grade DCIS and share a similar immunophenotype (9) although molecular studies indicate overlap in the genetic profiles of CCCA, DCIS, and invasive carcinoma (10). Therefore, views are shifting to consensus that CCCA probably represents the earliest recognizable lesion in the current model of human breast cancer progression (10,11).

Available evidence regarding the clinical significance of CCCA from the limited number of formerly published series is widely varied. The most recent, and largest series reported results similar to our findings: of 60 patients with "pure CCCA," 20 (33%) were found to have another advanced proliferative lesion after excision (8). The malignancy rate, however, was higher, being identified in eight patients (13%), six (10%) of whom had a finding of DCIS.

Two smaller series also found CCCA to be associated with other high-risk pathology in approximately one third of cases (3,12). One reported that other lesions were present in 9 of 14 (64%) cases with "pure" biopsies, including three instances (21%) of malignancy (12). In another study, 23 of 35 (66%) "pure CCCA" biopsies, resulted in the finding of five (14%) cases of malignancy (3). Reports involving unselected CCCA (i.e., when "non-pure" biopsies are included) have demonstrated other adjacent pathology in up to 60% cases and malignancy in 18% (13,14).

The small mean size of the index abnormality in our series is comparable to that reported by others and is consistent with the view that CCCA represents an early pathologic alteration (5,12). It is widely recognized that CCCA is most frequently associated with microcalcifications (5,12). However, the current series also confirms that CCCA may, less frequently, be detected as a sonographic abnormality (15). Ideally our report would have benefited from having a control group of columnar cell change without atypia, however, this was not possible given that lesions without atypia do not usually progress to formal excision. One previous study included excision data from columnar cell lesions without atypia, however, indications for excision and the location of subsequent pathology were not clear (6).

Our series also demonstrated the finding of primary breast malignancy a distant site in a further five (10%) patients. Only one previous study provided some limited data on the possible natural history of CCCA. They reported that 26 patients of 63 cases with "pure CCCA" initially identified on core biopsy underwent subsequent excision up to 10 years later with findings

of invasive carcinoma in seven patients (11%) in the ipsilateral breast and two patients (3%) on the contralateral side (4). They concluded that CCCA is a marker of increased risk for development of breast carcinoma and recommended close follow-up.

CONCLUSION

This study, which analyzes the subsequent surgical excision findings, after a diagnosis of "pure CCCA" on breast core biopsy, substantially contributes to the small number of reported series on this topic. Excision demonstrated that another pathologic lesion was found in the region of the core in approximately one third of cases, including malignancy in 6%, but a simultaneous breast cancer was also diagnosed at an alternative site in a further 10% of cases. The former finding supports the notion that CCCA is a precursor lesion of breast neoplasia, whereas the latter suggests that the entity of CCCA can also be viewed as a marker for breast cancer risk in general. We support the dictum that when CCCA is found on breast core biopsy, an open surgical biopsy of the relevant area should be performed. We would also recommend that thorough workup of both breasts be undertaken to exclude co-existent breast carcinoma at alternative sites, and that subsequent longer term breast screening be instigated.

CONFLICT OF INTEREST

There are no conflicts of interest to declare.

REFERENCES

1. Schnitt SJ. Flat epithelial atypia – classification, pathologic features and clinical significance. *Breast Cancer Res* 2003;5:263–8.

2. Moinfar F. Flat ductal intraepithelial neoplasia of the breast; A review of diagnostic criteria, differential diagnoses, molecular-genetic findings, an clinical relevance – it is time to appreciate the Azzopardi concept! *Arch Pathol La Med* 2009;133:879–92.

3. Chivukula M, Bhargava R, Tseng G, Dabbs DJ. Clinicopathologic implications of "flat epithelial atypia" in core needle biopsy specimens of the breast. *Am J Clin Pathol* 2009;131:802–8.

4. Martel M, Barron-Rodriguez P, Ocal IT, Dotto J, Tavassoli FA. Flat DIN 1 (flat epithelial atypia) on core needle biopsy: 63 cases identified retrospectively among 1,751 core biopsies performed over an 8year period (1992-1999). *Virchows Arch* 2007;451: 883–9.

5. Piubello Q, Parisi A, Eccher A, Barbazeni G, Franchini Z, Iannuci A. Flat epithelial atypia on core needle biopsy; Which is the right management? *Am J Surg Pathol* 2009;33:1078–84.

6. Ingegnoli A, D'Aloia C, Frattaruolo A, *et al.* Flat epithelial atypia and atypical ductal hyperplasia: carcinoma underestimation rate. *Breast J* 2010;16:55–9.

7. Lee T, Macintosh RF, Rayson D, Barnes PJ. Flat epithelial atypia on breast needle core biopsy: a retrospective study with clinical-pathological correlation. *Breast J* 2010;16:377–83.

8. Lavoue V, Roger CM, Poilblanc M, *et al.* Pure flat epithelial atypia (DIN 1a) on core needle biopsy: study of 60 biopsies with follow-up surgical excision. *Breast Cancer Res Treat* 2011;125: 121–6.

9. Jara-Lazaro AR, Tse GM, Tan PH. Columnar cell lesions of the breast: an update and significance on core biopsy. *Pathology* 2009;41:18–27.

10. Simpson PT, Gale T, Reis-Filho JS, *et al.* Columnar cell lesions of the breast: the missing link in breast cancer progression? *Am J Surg Pathol* 2005;29:734–46.

11. Bombonati A, Sgroi DC. The molecular pathology of breast cancer progression. *J Pathol* 2011;223:307–17.

12. Kunju LP, Kleer CG. Significance of flat epithelial atypia on mammotome core needle biopsy: should it be excised? *Hum Pathol* 2007;38:35–41.

13. Datrice N, Narula N, Maggard M, *et al.* Do breast columnar cell lesions with atypia need to be excised? *Am Surg* 2007;73:984–6.

14. Guerra-Wallace MM, Christensen WN, White RL. A retrospective study of columnar alteration with prominent apical snouts and secretions and the association with cancer. *Am J Surg* 2004;188:395–8.

15. Kim MJ, Kim EK, Oh KK, Park BW, Kim H. Columnar cell lesions of the breast: mammographic and US features. *Eur J Radiol* 2006;60:264–9.