The Korean Journal of Pathology 2009; 43: 301-5
DOI: 10.4132/KoreanJPathol.2009.43.4.301

Columnar Cell Lesions in Fibrocystic Change of the Breast: The Incidence and Relationship with Microcalcifications

Soo Im Choi · Hye Kyoung Yoon[1]

Department of Pathology, College of Medicine, Inje University, Dongrae Paik Hospital; [1]Pusan Paik Hospital, Busan, Korea

Received : November 26, 2008
Accepted : March 20, 2009

Corresponding Author
Soo Im Choi, M.D.
Department of Pathology, College of Medicine, Inje University, Dongrae Paik Hospital, 223-83 Bugok 3-dong, Geumjeong-gu, Busan 609-819, Korea
Tel: 051-607-8278
Fax: 051-512-2966
E-mail: withsooim@yahoo.co.kr

*This work was supported by the 2006 Inje University research grant.

Background : Columnar cell lesions (CCLs) are characterized by the presence of columnar epithelial cells lining the terminal duct lobular units of the breast and frequently found in biopsies for microcalcifications. Their incidence and relationship with other lesions and the locations of microcalcifications have not been established. **Methods :** We reviewed 1,038 cases of fibrocystic change (FCC) for the degrees of CCLs and ductal proliferative change (PC) and the locations of microcalcifications. **Results :** Among 1,038 FCC cases, CCLs were found in 18.9%, columnar cell change (CCC) in 12.5%, columnar cell hyperplasia (CCH) in 5.3% and flat epithelial atypia (FEA) in 1.1%. CCLs were found in 14.2%, 28.8%, and 40.0% of non-PC (NPC), proliferative disease (PD) without atypia and PD with atypia, respectively. Microcalcifications were found in 33.5%, 56.2%, 61.8%, and 81.8% of caese without CCLs, with CCC, CCH and FEA, respectively. Their locations were in NPC in 66.3% of the cases, PD in 14.8% of the cases or both areas in 18.8% of FCC. **Conclusions :** The incidence of CCLs increased according to the degree of PD without positive correlation between the degree of CCLs and PD. The frequency of microcalcifications increased according to the degree of CCLs but was statistically insignificant. There is a possibility that a needle biopsy targeting a microcalcification area might leave additional PD around the targeted area because microcalcifications were found more frequently in NPC than PD area.

Key Words : Fibrocystic breast disease

Since columnar cell lesions (CCLs) were first described in the literature by Foote in 1945[1] as blunt duct adenosis, they were known by various names such as columnar cell metaplasia,[2] atypical lobule type A,[3] monomorphic type of clinging carcinoma,[4] columnar alteration of lobule,[5] cancerization of small ectatic ducts,[6] columnar alteration with prominent apical snouts and secretions,[7] atypical cystic lobule,[8] columnar cell change (CCC) and hyperplasia (CCH),[9] atypical cystic duct,[10] flat epithelial atypia (FEA),[11] and enlarged lobular unit with columnar alteration.[12] They are characterized by a presence of columnar shaped epithelial cells lining terminal duct lobular units without or with variable degrees of epithelial hyperplasia and recently classified as CCC, CCH and CCH with atypia (FEA) according to the degree of cellular hyperplasia and nuclear atypia.[13-18] They are increasingly found in biopsies taken for microcalcifications on mammography, but their incidence among benign breasts and the relationship between CCLs and microcalcifications or ductal hyperplasia (DH) are not established yet. They are assumed to be associated with lobular or ductal lesions of breast and have an increased risk for cancer when accompanied by atypia.[9,13,14,19-23]

Therefore, we investigated the incidence of this lesion among fibrocystic change (FCC) and its relationship with ductal proliferative disease (PD) and with microcalcifications.

MATERIAL AND METHODS

The files of Inje University Pusan Paik Hospital, Department of Pathology were searched for FCC diagnosis by excisional biopsy or mammotome excision from January to December, 2004. We excluded the cases with accompanying fibroadenoma, papilloma or inflammatory lesions. H&E stained slides were reviewed by two pathologists for the presence and degrees of CCLs, the degrees of accompanying PD, and the presence and locations of microcalcifications. CCLs were classified into CCC, CCH and FEA according to Schnitt and Vincent-Salomon (Fig. 1).[24] The degrees of PD were classified into non-proliferative change (NPC), PD without atypia PD with atypia according to Kumar *et al*.[25] The locations of microcalcifications were classified into 'PD' when microcalcifications were within the areas of PD, 'NPC' when

they were in area of NPC, 'both' when they were in both PD and NPC areas (Fig. 1).

Statistical analysis

For statistical evaluation, the relationships were assessed by chi-square test using the SAS 8.0 statistical software program (SAS Institute, NC, USA). And the trend was assessed by chi-square test for trend using MedCalc ver.10.0.2 (Medcalc Software bvba, Mariakerke, Belgium). A p-value below 0.05 was considered as statistically significant.

RESULTS

A total of 1,038 cases of FCC without or with PD excluding cases with accompanying neoplastic or inflammatory conditions were reviewed.

The incidence of CCLs among FCC

CCLs were found in 196 (18.9%) cases of FCC out of a toatal of 1,038 cases. CCC, CCH and FEA were found in 130 (12.5%), 55 (5.3%) and 11 (1.1%) cases of FCC, respectively (Table 1).

Table 1. Relationship between the degree of ductal proliferation and the degree of columnar cell lesions

	NPC (%)	PD without A (%)	PD with A (%)
No CCLs (842)[a]	630 (85.8)	188 (71.2)	24 (60.0)
CCLs (196)[a]	104 (14.2)	76 (28.8)	16 (40.0)
CCC (130)[b]	73 (70.2)	49 (64.5)	8 (50.0)
CCH (55)[b]	27 (26.0)	21 (27.6)	7 (43.8)
FEA (11)[b]	4 (3.9)	6 (7.9)	1 (6.3)

[a]p<0.0001 (chi-square test for trend); [b]p=0.4361.
CCLs, columnar cell lesions; CCC, columnar cell change; CCH, columnar cell hyperplasia; FEA, flat epithelial atypia; NPC, non-proliferative breast changes; PD, proliferative disease; A, atypia.

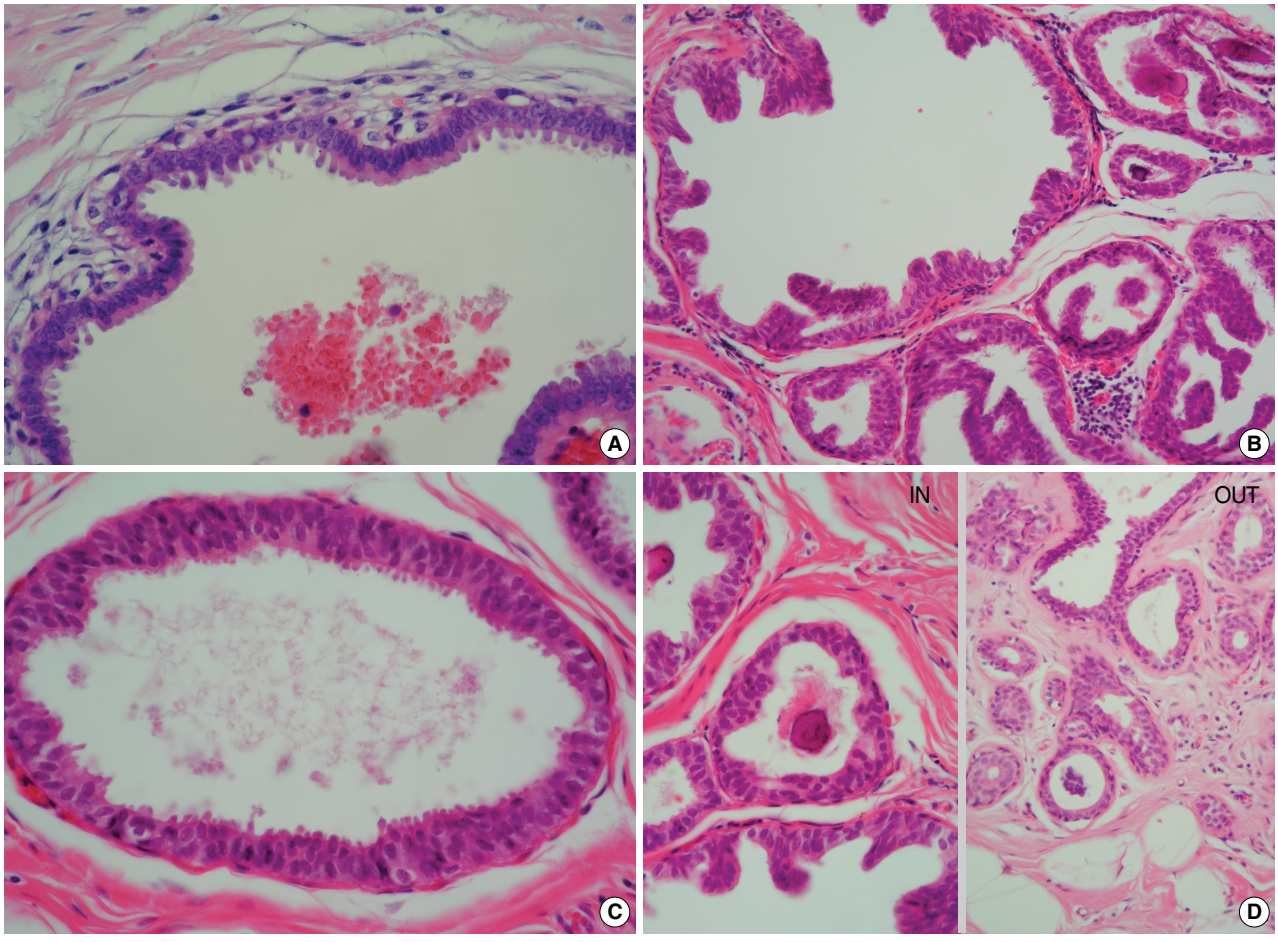

Fig. 1. (A) Columnar cell change, (B) columnar cell hyperplasia, (C) flat epithelial atypia, (D) microcalcifications within (left) and outside (right) lesions are shown.

The relationship between CCLs and PD among FCC

The incidence of CCLs increased to 104 (14.2%), 76 (28.8%) and 16 (40.0%) for NPC, PD without atypia and PD with atypia, respectively (p<0.0001, chi-square test for trend), but there was no correlation between the degrees of CCLs and degrees of PD (p=0.4361) (Table 1).

Relationship between CCLs and microcalcifications

Microcalcifications were found in 398 cases (38.3%) of FCC. They were more frequently found in cases with CCLs (59.2%) than in cases without them (33.5%) (p<0.0001). Their frequency increased to 282 (33.5%), 73 (56.2%), 34 (61.8%), and 9 (81.8 %) for cases without CCLs, with CCC, CCH and FEA, respectively (p<0.0001, chi-square test for trend). But among CCLs, there was no correlation between the degrees of CCLs and the presence of microcalcifications (p=0.2248, chi-square test for trend) (Table 2).

The locations of microcalcifications

Microcalcifications were found in NPC in 264 cases (66.3%), in PD in 59 cases (14.8%) or in both areas in 75 cases (18.9%) of FCC. They were more frequently found in the area of NPC (49 cases, 42.2%) than within PD (25 cases, 22.4%) of CCLs and these findings were more pronounced among cases without CCLs having 215 cases (76.2%) in the NPC area and 33 cases (11.7%) within PD area (Table 3).

DISCUSSION

CCLs consist of a spectrum of changes to the terminal duct lobular unit of the breast ranging from bland columnar alteration through CCH to FEA. The classification of these lesions was not established yet, and recently Schnitt proposed a system consisting of four categories and later simplified it into three categories. CCC is a variable dilation of the terminal duct lobular unit lined by one or two layers of uniform ovoid to elongated nuclei oriented perpendicular to the basement membrane. CCH shows a cellular stratification with more than two cell layers without complex architectural patterns. They may show prominent apical snouts, luminal secretions and microcalcifications. FEA shows epithelial cells replaced by one to several layers of monotonous, atypical cuboidal to columnar cells. The degree of atypia is subtle and falls short of diagnosis for atypical DH.

In 1945, Foote and Stewart stated that blunt duct adenosis was found in 26% of non-cancerous and 26% of cancerous breasts.[1] Since then their incidence rate is not known. These lesions, especially bland CCC, are difficult to notice by microscopic examination on a low power view. We found CCLs in 18.9% of FCC. CCC, CCH and FEA were found in 12.5%. 5.3%, and 1.1% of FCC, respectively.

Although the significance of CCLs have not been reported in the literature yet, it is assumed that they, especially FEA, are morphologic initial steps or precursors to ductal carcinoma *in situ*,[14,19,21,23,26] or associated with lobular neoplasia or tubular carcinoma.[9,13,20,22] Since we confined this study to benign lesions, the relationship with malignancy cannot be determined. In our study, the incidence of CCLs was higher when the degree of proliferation was higher, but there was no positive correlation between the degree of CCLs and the degree of PD (p=0.4361). The cases accompanying lobular hyperplasia were also found in 7 out of 1,038 cases, and 2, 2, 2, and 1 cases were without CCLs, with CCC, CCH, and FEA, respectively. As the cases with lobular carcinoma *in situ* or invasive lobular carcinoma were not included in our study which was done with benign lesions and their numbers are so few, we cannot determine the relationship between the degree of lobular hyperplasia and CCLs.

Table 2. Relationship between the presence and degree of columnar cell lesions and microcalcifications

	No MC (%)	MC (%)
No CCLs (842)[a]	560 (66.5)	282 (33.5)
CCLs (196)	80 (40.8)	116 (59.2)
CCC (130)[a,b]	57 (43.8)	73 (56.2)
CCH (55)[a,b]	21 (38.2)	34 (61.8)
FEA (11)[a,b]	2 (18.2)	9 (81.8)

[a]p<0.0001 (chi-square test for trend); [b]p=0.1147 (chi-square test for trend).
CCLs, columnar cell lesions; MC, microcalcifications.

Table 3. Relationship between the presence of columnar cell lesions and the location of microcalcification

	NPC[a] (%)	PD[b] (%)	Both[c] (%)
No CCLs (282)	215 (76.2)	33 (11.7)	34 (12.1)
CCLs (116)	49 (42.2)	26 (22.4)	41 (35.4)
Total (398)	264 (66.3)	59 (14.8)	75 (18.9)

[a]present in non-proliferative area; [b]present in proliferative area; [c]present in both non-proliferative and proliferative areas.
CCLs, columnar cell lesions; PD, proliferative disease; NPC, non-proliferative breast changes.

CCLs were more frequently found in biopsies taken for microcalcifications on mammography. It is reported that CCLs were found in 42% of the cases with microcalcifications on mammography and microcalcifications were found in 74% of columnar alteration with prominent apical snouts and secretions.[7] In our study, microcalcifications were found in 38.3% of FCC. They were more frequently found in FCC with CCLs (59.2%) than FCC without them (33.5%) ($p<0.0001$). The frequency of microcalcifications increased when the degree of CCLs were higher, from 33.5% of without CCLs, 56.2% of CCC, 61.8% of CCH to 81.8% in FEA ($p<0.0001$, chi-square test for trend), but among CCLs, the degrees of CCLs and the presence of microcalcifications were not positively correlated statistically ($p=0.1147$, chi-square test for trend).

It is reported that in malignant lesions, microcalcifications were found within tumor lesions, next to tumor, or both in 63%, 5%, and 33%, respectively.[27] In another study, the locations of microcalcifications were correlated with lesions such as atypical DH, *in situ* or invasive ductal carcinoma in 52.4%.[28] Cox *et al*. compared the cores with and without microcalcifications on specimen radiography and the result was that in core biopsy without microcalcifications, 25% contained B3-B5 pathology (suspicious for or malignant lesions).[29] We compared the locations of microcalcifications between areas of PD such as CCH, FEA, moderate to atypical DH, and remaining NPC area. Microcalcifications were more frequently found in NPC areas (66.3%) than PD areas (14.8%) of FCC. The difference was more pronounced among cases without CCLs as 76.2% in NPC and 11.7% in PD than among the cases with CCLs as 42.2% in NPC area and 22.4% in PD area (Table 3). In cases showing only NPC such as slight dilatation of acini or ducts with apocrine metaplasia and microcalcifications on needle biopsy, there is a possibility that further PD may have remained around the targeted focus of microcalcifications.

In conclusion, the incidence of CCLs among FCC is 18.9% and their frequency increased when the degree of PD was higher but there was no statistically significant positive correlation between the degree of PD and the degree of CCLs. Microcalcifications were found more frequently in cases with CCLs than without them and the frequency of them increased according to the degree of CCLs, but the differences were not statistically significant. Microcalcifications were found in NPC as well as in PD areas, and there is a possibility that additional PD may be present in areas around the targeted site of microcalcifications when a needle biopsy targeted for microcalcifications showed only NPC. In cases showing only NPC histologically targeted for microcalcification site, additional evaluation will be needed to detect further or undetected lesions.

REFERENCES

1. Foote FW, Stewart FW. Comparative studies of cancerous versus noncancerous breasts. Ann Surg 1945; 121: 6-53.
2. Bonser G, Dossett JA, Jull W. Human and experimental breast cancer. London: Pitman Medical, 1961.
3. Wellings SR, Jensen HM, Marcum RG. An atlas of subgross pathology of the human breast with special reference to possible precancerous lesions. J Natl Cancer Inst 1975; 55: 231-73.
4. Azzopardi J. Problems in breast pathology. Philadelphia: WB Saunders, 1979.
5. Page DL, Anderson TJ. Diagnostic histopathology of the breast. Edinburgh, Scotland: Churchill Livingstone, 1987.
6. Goldstein NS, O'Malley BA. Cancerization of small ectatic ducts of the breast by ductal carcinoma in situ cells with apocrine snouts: a lesion associated with tubular carcinoma. Am J Clin Pathol 1997; 107: 561-6.
7. Fraser JL, Raza S, Chorny K, Connolly JL, Schnitt SJ. Columnar alteration with prominent apical snouts and secretions: a spectrum of changes frequently present in breast biopsies performed for microcalcifications. Am J Surg Pathol 1998; 22: 1521-7.
8. Oyama T, Maluf H, Koerner F. Atypical cystic lobules: an early stage in the formation of low-grade ductal carcinoma in situ. Virchows Arch 1999; 435: 413-21.
9. Rosen PP. Columnar cell hyperplasia is associated with lobular carcinoma in situ and tubular carcinoma. Am J Surg Pathol 1999; 23: 1561.
10. Kusama R, Fujimori M, Matsuyama I, *et al*. Clinicopathological characteristics of atypical cystic duct (ACD) of the breast: assessment of ACD as a precancerous lesion. Pathol Int 2000; 50: 793-800.
11. Schnitt SJ. The diagnosis and management of pre-invasive breast disease: flat epithelial atypia- classification, pathologic features and clinical significance. Breast Cancer Res 2003; 5: 263-8.
12. McLaren BK, Gobbi H, Schuyler PA, *et al*. Immunohistochemical expression of estrogen receptor in enlarged lobular units with columnar alteration in benign breast biopsies: a nested case-control study. Am J Surg Pathol 2005; 29: 105-8.
13. Abdel-Fatah TM, Powe DG, Hodi Z, Lee AH, Reis-Filho JS, Ellis IO. High frequency of coexistence of columnar cell lesions, lobular neoplasia, and low grade ductal carcinoma in situ with invasive tubular carcinoma and invasive lobular carcinoma. Am J Surg Pathol 2007; 31: 417-26.

14. Dabbs DJ, Carter G, Fudge M, Peng Y, Swalsky P, Finkelstein S. Molecular alterations in columnar cell lesions of the breast. Mod Pathol 2006; 19: 344-9.
15. Noel JC, Fayt I, Fernandez-Aguilar S, Buxant F, Boutemy R. Proliferating activity in columnar cell lesions of the breast. Virchows Arch 2006; 449: 617-21.
16. Pandey S, Kornstein MJ, Shank W, de Paredes ES. Columnar cell lesions of the breast: mammographic findings with histopathologic correlation. Radiographics 2007; 27 (Suppl 1): S79-89.
17. Polat A. c-KIT expression in columnar cell lesions of the breast accompanied by benign and malignant breast diseases. Pathol Res Pract 2007; 203: 765-9.
18. Feeley L, Quinn CM. Columnar cell lesions of the breast. Histopathology 2008; 52: 11-9.
19. Lee S, Medina D, Tsimelzon A, *et al*. Alterations of gene expression in the development of early hyperplastic precursors of breast cancer. Am J Pathol 2007; 171: 252-62.
20. Leibl S, Regitnig P, Moinfar F. Flat epithelial atypia (DIN 1a, atypical columnar change): an underdiagnosed entity very frequently coexisting with lobular neoplasia. Histopathology 2007; 50: 859-65.
21. Oyama T, Iijima K, Takei H, *et al*. Atypical cystic lobule of the breast: an early stage of low-grade ductal carcinoma in-situ. Breast Cancer 2000; 7: 326-31.
22. Sahoo S, Recant WM. Triad of columnar cell alteration, lobular carcinoma in situ, and tubular carcinoma of the breast. Breast J 2005; 11: 140-2.
23. Simpson PT, Reis-Filho JS, Gale T, Lakhani SR. Molecular evolution of breast cancer. J Pathol 2005; 205: 248-54.
24. Schnitt SJ, Vincent-Salomon A. Columnar cell lesions of the breast. Adv Anat Pathol 2003; 10: 113-24.
25. Kumar V, Abbas AK, Fausto N. Robbins and Cotran Pathologic basis of disease. Philadelphia: Elsevier, 2005.
26. Simpson PT, Gale T, Reis-Filho JS, *et al*. Columnar cell lesions of the breast: the missing link in breast cancer progression? A morphological and molecular analysis. Am J Surg Pathol 2005; 29: 734-46.
27. Homer MJ, Safaii H, Smith TJ, Marchant DJ. The relationship of mammographic microcalcification to histologic malignancy: radiologic-pathologic correlation. AJR Am J Roentgenol 1989; 153: 1187-9.
28. Johnson JM, Dalton RR, Wester SM, Landercasper J, Lambert PJ. Histological correlation of microcalcifications in breast biopsy specimens. Arch Surg 1999; 134: 712-5.
29. Cox D, Bradley S, England D. The significance of mammotome core biopsy specimens without radiographically identifiable microcalcification and their influence on surgical management- a retrospective review with histological correlation. Breast 2006; 15: 210-8.