

## Clinical Significance of Mucin Extravasation in Breast Core Biopsy Specimens

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### ABSTRACT

Mucin extravasation (ME) refers to the presence of mucin pools in the breast parenchyma, usually resulting from ruptured ducts distended with luminal mucin. Extravasated mucin is usually seen along with cystically dilated mucin filled ducts or mucocele like lesions (MLL) of the breast. MLL is a rare lesion that may be associated with a continuum of benignity to invasive mucinous carcinoma. The purpose of this study was to document the spectrum of lesions that can be associated with ME in breast cores and to correlate with the histology in subsequent surgical excision.

Thirty-seven cases with ME on image guided core biopsies were reviewed from our departmental files, and their radiologic histologic findings were noted. Twenty-six of them of them underwent subsequent open biopsies which forms the basis of this study.

It was noticed that columnar cell lesion (CCL) associated with mucocele like lesion (MLL) as an important finding in relation with atypia. This finding was significant regardless of their presence in calcified or non-calcified cores and also a very good statistical correlation was seen between the quantitative presence of CCL in the core and excisional biopsy diagnosis.

This are support the need for excision biopsy for the cases presenting with ME in their cores. In addition, a multidisciplinary approach should also be taken for cases presenting with ME, MLL and CCL altogether in breast core biopsies even in absence of obvious cytological atypia.

**Key Words:** Mucin Extravasation, Columnar Cell Lesion (CCL), Mucocele Like Lesion (MLL), Fibrocystic Change (FCC), Atypical Ductal Hyperplasia (ADH), Ductal Carcinoma in Situ (DCIS)

### Introduction

Mucin extravasation (ME) is a term expressed for extrusion of mucin into the surrounding stroma. These are the extracellular mucoid substances of epithelial origin<sup>1</sup>. ME is usually seen in the vicinity of cystically dilated mucin filled duct which constitutes mucocele like lesions (MLL)<sup>2</sup>. MLLs are defined by Rosen<sup>3</sup> as mucin-containing cysts lined by flat or low cuboidal epithelium, with or without extravasated mucin. The lesions were initially considered entirely benign, but subsequent experience has shown that it may not always

be so<sup>2,4</sup>. The spectrum of breast lesions that demonstrate mucin also includes fibrocystic change with luminal mucin, MLL that range from benignity to those associated with atypical ductal hyperplasia (ADH) and ductal carcinoma in situ (DCIS), mucinous papillary lesions, mucinous carcinoma and other conditions accompanied by stromal mucosubstances and mucin-like material<sup>5</sup>. Several studies have supported the association of MLL of the breast with atypical ductal hyperplasia or carcinoma<sup>6,7,8</sup>. Cribriform and micropapillary ductal carcinoma in situ (DCIS) and invasive

carcinoma, usually of the mucinous type, have been reportedly associated<sup>6,7</sup>.

Accurate diagnosis of mucinous lesions on core biopsy specimens may be challenging, especially when the associated epithelial lesion is borderline, or if only part of the proliferating epithelial lesion has been sampled. We report in this series core biopsies with ME, with or without accompanying epithelial abnormality and correlate with their subsequent excisions.

### Materials And Methods

Records of all breast core biopsy specimens with the terms “mucin extravasation” or “mucocele like lesion” from December, 2003 through September, 2008 were retrieved from the surgical pathology database files at our institution. Slides were reviewed and correlated with those of the subsequent excision biopsy.

All breast core needle biopsy specimens were obtained by the radiologists who had been accredited for the procedure according to our institutional guidelines. The procedure consisted almost exclusively (n=35) of stereotactic mammotome biopsy (VABB) by using 11-gauge needle except in one in which a 14-gauge needle was used for VABB. In four cases procedure was done under ultrasound guidance and by conventional mammotome method using 11 gauge automated needle. Of the remaining two cases, information about the needle size or procedure was not available. The radiologist performing the procedure kept a metallic marker at biopsy site in the event that calcifications were completely removed or were extremely faint. Cores were separated into those with and without calcifications and placed in labeled containers before submitting for histological examination.

All samples were routinely processed and studied histologically. In total 39 lesions of 37 patients were examined. All lesions in this series had ME into stroma. These patients were advised to undergo wire localized surgical excision. Out of 37 cases, 26 underwent excisional biopsy. The core biopsies were reviewed and compared with the subsequent surgical excisions. Histological

diagnosis of CCL, ADH or DCIS followed standard guidelines<sup>7,9</sup>. CCL includes a spectrum of lesions ranging from bland columnar cell alteration to columnar cell hyperplasia with atypia. At present there is no internationally accepted classification or terminology for this range of lesion although there are some recommendations. Peter T Simpson et al.<sup>10</sup> described histological features of the different categories of CCLs. The authors have subdivided these lesions into six different types; such as columnar cell change (CCC), CCC with Cytologic atypia, columnar cell hyperplasia (CCH), CCH with architectural atypia, CCH with cytologic atypia, and CCH with architectural and cytologic atypia. ADH and low nuclear grade DCIS are closely related lesions, with histological distinction based on cytoarchitectural features and lesional extent<sup>5</sup> ADH was diagnosed on core biopsy when atypical epithelial alterations exhibited both cytological and architectural features of low-grade non-comedo DCIS, but measuring less than 2mm or affecting not more than two duct spaces<sup>11,12</sup>. Core biopsy cases were classified into different categories --

- A) Those with ME and benign epithelial changes not otherwise specified.
- B) Those with ME and benign epithelial changes including CCL.
- C) Those with ME and benign epithelial changes including both CCL and ADH.
- D) Those with ME and adjacent DCIS, and
- E) Those with mucin and either adjacent invasive carcinoma or islands of detached epithelial cells diagnostic of mucinous carcinoma.

Additionally for each case the number of cores showing these features were noted. In cases of CCL, ADH and DCIS their presence or absence in the same core along with ME were noted. For DCIS its subtype was noted and its extent was measured in core biopsy sections. Other associated histologic changes were tabulated. Core biopsy findings were scored as-M-1-ME in only one core. M-2- ME in more than one core; M-3 - MLL in one core only; M-4- MLL in more then one core; M-5-ME accompanied with CCL; M-6-ME not accompanied with CCL; M-7 - CCL in only one core; M-8- CCL in more then one core.

M1 and M2 explains the extent of ME only in the cores regardless of their association with mucin filled distended ducts. In M3 and M4 extent of mucin filled distended ducts on the cores were noted down regardless of their association with ME. M5 and M6 expresses whether CCL had adjacent ME in the same core or not. M7 and M8 explains extent of CCL in the cores.

Among 37 patients having mucin extravasations in their core biopsies, 26 had undergone excisional biopsy follow up and forms the basis of this report.

Final diagnosis of core and excisional biopsies were termed as Fibrocystic change(FC); FC with ADH; DCIS & Invasive carcinoma.

## Results

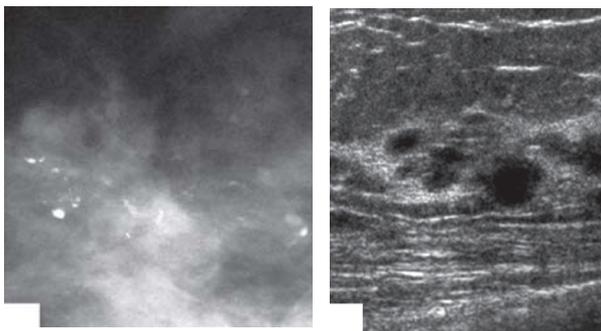
### *Patient Demographics*

Thirty-nine lesions in thirty-seven patients were included in the study. Of these thirty-two were Chinese, four Malay and one Indian. The mean patient age was 48.2 years. Age range was between 41 to 62 years. One patient had bilateral involvement and in another there was involvement of two sites of the same breast. All the lesions in these two cases showed ME in their cores. Twenty lesions were observed in the right breast and nineteen in the left. Twenty lesions were present in the upper & outer quadrant of breasts, three each at lower outer quadrant, 6 O' clock and 12 O'clock positions; two each at lower inner quadrant and retroareolar positions and one each at 3 O' clock and 9O' clock positions. In one case there was bilateral involvement and in another two separate lesions were detected in the same breast.

### **Imaging Characteristics**

All the lesions (except one) were mammographically detected on routine breast screens. Microcalcifications (Fig1) constituted the dominant radiological abnormality being observed in 37 (94.8 %) of total 39 lesions in 37 patients. Only one of our cases presented with a palpable breast mass which showed coarse calcifications in mammogram. Rest of the patients (n=36) were asymptomatic who had participated in a nationwide breast screening program to which women

were recalled for further investigation after an abnormal screening mammogram. In thirty-four lesions core biopsies were performed for presence of calcification and in five (including the palpable mass) for nodular presentations. The nodules (n=4) ranged from 0.7 to 1.1 cm. at dimension ( Fig 2) ; of which two showed areas of calcification. The extent of the palpable lesion is however, not known.



**Fig 1:** Microcalcifications (Mammographic view)

**Fig 2:** Nodular lesion (Mammographic view)

In 56.8 % (n=21) lesions all calcified zones were completely removed by the biopsy procedure; however in 43.2 % (n=16) of them calcifications were not completely removed.

Number of cores per each breast biopsy ranged from 1 to 27 cores or core fragments. More than 12 cores or core fragments were examined in 29 cases.

## **Pathological Findings**

### *Core Biopsies*

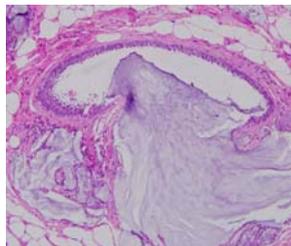
All the core biopsy specimens except one had mucin extravasation into the connective tissue with further epithelial lined mucin distended structures adjacent to them fulfilling the criteria of mucocele like lesion. In a single case, the core biopsy tissue was composed entirely of mucin pools ( Fig 5 )without any epithelial cells floating into it. As to compare with the status of complete removal of calcium and core biopsy diagnosis, no statistically significant correlation ( $p=0.79$ ) was found. Table I

shows the Cross tabulation of core biopsy result with calcium removal status.

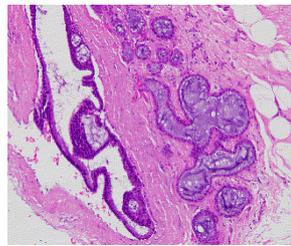
**Table I :** Cross tabulation of core biopsy result with calcium removal status (p value 0.79)

Core Biopsy Diagnosis	Calcium Removal Status			Total
	Residual Calcification Present	Calcium Completely Removed	Noncalcified Lesion	
	Mucin pool only	1	0	
Fibrocystic Change	5	15	1	21
FC WITH ADH	7	5	1	13
DCIS	3	1	0	4
<b>Total</b>	<b>15</b>	<b>11</b>	<b>2</b>	<b>39</b>

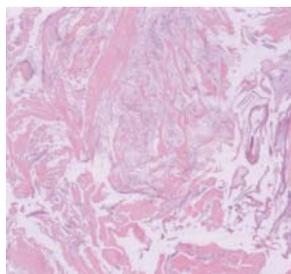
There was microscopic evidence of microcalcification within the mucinous secretion or embedded in the connective tissue stroma of all the cores, radiologically specified as calcified cores. ME was seen in 69.2 % (n=27) of samples radiologically described as “calcified cores” and in 15.4 % (n=6) of those described as “non-calcified cores.” In six others (15.4%) extravasated mucin was found in both calcified and non-calcified cores. No statistically significant correlation was however detected between presence of ME in the calcified core and the final core biopsy diagnosis. Table II shows the core biopsy results.



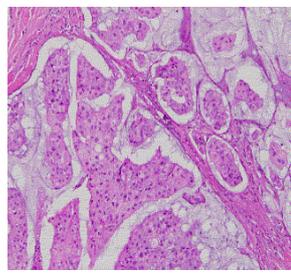
**Fig 3:** Columnar cell change (H&EX40)



**Fig 4:** Atypical ductal hyperplasia(H&EX40)



**Fig 5:** Mucin extravasation (H&EX10)



**Fig 6:** Mucinous carcinoma(H&E X10)

**Table II :** Core biopsy result of all thirty-nine lesions.

Core Biopsy Diagnosis				
Mucin Pool Only	Fibrocystic Change	Fibrocystic Change With ADH	Ductal Carcinoma In Situ	Total
1	20	13	5	39

On core needle biopsy (CNB) less than half of the lesions (46.2%) were diagnosed as atypia including ADH, DCIS and invasive carcinoma. Twenty-one CNB lesions (53.8%) were histologically benign. The group included FC without any specification, and FC with CCL(Fig 3). Thirteen cases (33.3%) had features of ADH (Fig 4) along with FC and four (10.3%) were diagnosed as low grade DCIS. One of our patients had bilateral benign synchronous ADH. Another case had FC in two separate lesions at the same breast. It was also noted that ADH was present in non-calcified cores of seven of our CNB cases. Of these 5 showed ADH exclusively on the non-calcified cores. In additional two cases DCIS was found in both calcified and non-calcified cores. These were of low grade micropapillary type; their extent ranged from 2.5 mm to 6 mm and they also had accompanying MLL and CCL along with the atypia.

In cases where follow up excision biopsy diagnoses were available(n=27), CCL s were seen in 84.6% (n = 33) of their cores. In 53.8 % (n=21) cases CCL was seen in more than one core. This observation had significant correlation with diagnostic outcome of subsequent Excision. Twelve of thirteen cases diagnosed as FC with ADH and all four cases of DCIS had CCL involving two or more cores. This finding was also statistically significant (p= 0.005).

### Excision biopsies

On excision more than half of the lesions (70.2%) were diagnosed with atypia including ADH, DCIS and invasive carcinoma. One case presented with invasive mucinous carcinoma (Fig 6). Five (18.5%) were diagnosed as DCIS; four of them were of low grade micropapillary type and one was low to intermediate grade micropapillary and cribriform type. and extended from 2.5 mm to 1.8 cm. at excision. As to compare with the status of

complete removal of calcium and excisional biopsy diagnosis, the findings were again not statistically significant ( $p=0.30$ ). TABLE III shows the crosstabulation between excision biopsy diagnosis and calcium removal status of mammotome biopsy procedure. Thirteen cases (48.1 %) were diagnosed as FC with ADH and nine (33.3%) had FC alone. 73.7% ( $n=14$ ) of our cases finally diagnosed as ADH / DCIS or invasive malignancy had their lesions in upper quadrant of the breast. However, no good statistical correlation was seen between the diagnosis and the site of the lesion.

**Table III:** Crosstabulation between excision biopsy diagnosis and calcium removal status during mammotome biopsy procedure ( $p$  value = 0.30).

Excisional Biopsy Diagnosis	Calcium Removal Status			Total
	Residual Calcification Present	Calcium Totally Removed	Noncalcified Lesion	
FC	4	4	0	8
FC with ADH	6	6	1	13
DCIS	4	1	0	5
Invasive Carcinoma	1	0	0	1
<b>Total</b>	<b>15</b>	<b>11</b>	<b>1</b>	<b>27</b>

In 11 of our patients in whom no follow up excision biopsy was recorded in our institution, remained free from breast malignancy till the cutoff period of June, 2008 as per our national cancer registry. Out of these eleven patients 12 lesions (one having two lesions in same breast) were biopsied (CNB), all of them were diagnosed as FC without any atypia. Areas of microcalcification were totally removed during biopsy procedure in 9 cases, incompletely removed in one and in the other there was a nodular presentation without calcification.

### Correlation of core with excision specimens

In total 4 of our cases were underdiagnosed on core biopsy; two of them were diagnosed as benign fibrocystic disease without atypia which were later described as FC with ADH. One case revealed piece of fibrous tissue dissected by pool

of acellular mucin was diagnosed as stromal mucin which ended up as invasive mucinous carcinoma at excision. Another one diagnosed as FCD with ADH was upgraded to DCIS at excision. Statistically significant correlation (Table IV) was found among the core biopsy and excision biopsy diagnosis ( $p < 0.001$ ).

**Table IV:** Comparison between core biopsy and excisional biopsy diagnosis ( $p$  value  $< 0.05$ )

Core Biopsy Diagnosis	Excisional Biopsy Diagnosis				Total
	FC	FC With ADH	DCIS	Invasive Carcinoma	
Mucin Pool	0	0	0	1	1
FC	8	1	0	0	9
FC With ADH	0	12	1	0	13
DCIS	0	0	4	0	4
<b>Total</b>	<b>8</b>	<b>13</b>	<b>5</b>	<b>1</b>	<b>27</b>

Mucocele like lesions, columnar cell changes and ADH when found were seen in the same core in all of our cases. ME and CCL together in the same core were found in all thirteen CNB lesions finally diagnosed as ADH on excision and also in all 5 cases with DCIS. About half of cases of ADH (53.8%) and DCIS (60%) diagnosed on excision had ME in two or more of their cores. On the other hand almost all cases of ADH (92.3%) or DCIS (100%) on excision had MLL extending through two or more of their respective cores. Table III shows the crosstabulation of different findings scored on core biopsies and compared with excisional biopsy result.

**Table V:** Cross tabulation of excision biopsy diagnosis with Columnar cell changes seen in the cores ( $p$  value  $< 0.005$ )

Excision Biopsy Diagnosis	No. Of Cores With CCL On CNB		Total
	Ccl In One Core	Ccl In More Than One Core	
FC	5	3	8
FC WITH ADH	1	12	13
DCIS	0	5	5
Invasive Carcinoma	0	1	1
<b>Total</b>	<b>6</b>	<b>21</b>	<b>27</b>

## Discussion

MLL, a rare lesion of the breast, can be asymptotically detected on a screening mammogram as microcalcifications or as a nodule. Although the lesion was originally reported as a benign entity, subsequent reports have shown an association with columnar cell changes, atypical hyperplasia and malignancy.<sup>4,6,12,13</sup> MLL and mucinous carcinoma may represent two ends of the pathological spectrum of mucinous lesions of the breast. Little data exists on mucinous lesions that may be considered intermediate between mucocele like tumour and invasive mucinous carcinoma. The spectrum of CCL characterized by variably enlarged terminal-duct lobular units lined by variably hyperplastic and variably atypical columnar cells has been the subject of discussion in the recent literature. Retrospective analysis by some authors have suggested that those with atypia as encompassed by Flat epithelial atypia (FEA), may represent a marker of a slightly increased risk for the subsequent development of invasive carcinoma when they are identified in a biopsy<sup>14</sup>.

In this series, benign lesions included fibrocystic changes (FC) alone and FC with columnar cell lesions (CCL). Some lesions were diagnosed as FC with atypical ductal hyperplasia's (ADH). We have seen CCL in all CNB specimens except 6 (15.4 %) cases. For practical purposes, CCLs were noted down in this series as a broad term. These can however be placed into one of three broad groups: Columnar cell change, columnar cell hyperplasia, and columnar cell change or hyperplasia with atypia. Very good statistical correlation ( $p < 0.005$ ) was found between cases showing CCLs extending through two or more cores and the presence of findings like ADH or DCIS on excision. CCL as we observed here was always found adjacent to MLL on the cores which suggest potential relationship between them. Moreover, MLL, CCL and ADH or DCIS whenever found were seen in the same core in all of our cases. This close association of MLL & CCL with low grade malignancy suggest a potential relationship between them also supported by some other authors.<sup>13,15</sup> These authors have also reported heterogenous and remarkably low proliferative indices among CCL and MLL.

As to compare with the lesions characterized with microcalcifications, no significant correlation ( $p=0.79$ ) was found between complete removal of calcium and diagnostic concordance of CNB with excision. biopsy. Moreover we detected ME, ADH and DCIS in calcified as well as non-calcified cores and in five of our cases ADH was detected exclusively in the non-calcified cores.

Twelve core biopsies of which no subsequent excision was available, follow up study showed that they did not develop any malignant breast lesion till June, 2008. From the unremarkable histological findings in their cores and as radiologically detectable calcifications were also totally removed in almost all of them, we can assume that no subsequent atypia developed in their breasts so far giving rise to a more sinister lesion.

12 of the 15 cases of ADH, DCIS and invasive carcinoma had their lesions at upper quadrant of breast. This finding however was not statistically significant.

The core biopsy diagnosis was significantly associated with subsequent excisional biopsy diagnosis ( $p$  value  $< 0.05$ ). Analysis of the excision specimens showed only fibrocystic changes in nine (34.6%) of our cases. Two excisional biopsies showed atypia (ADH) not detected in their corresponding core biopsies.

There were eleven cases (42.3%) of atypical ductal hyperplasia and six malignancies (23 %) finally detected in Excised specimens. When the 10 lesions demonstrating atypical ductal hyperplasia on core were excised, 9 of them were found to have residual ADH and one revealed DCIS. Two CNBs diagnosed as benign fibrocystic disease without atypia were later described as FC with ADH on excision.

Five of the six malignancies were DCIS of which four were of low nuclear grade and one of intermediate grade. Four of them were micropapillary and one both micropapillary and cribriform in type. Their extent ranged from 7 to 18 mm on excision. One patient was found to have invasive mucinous carcinoma, and this was the patient in whom CNB showed only mucin pools.

## Conclusion

From our histological data we may conclude like many authors that ME, CCL, ADH, DCIS and Invasive mucinous carcinoma constitutes a pathologic spectrum of a low to intermediate grade malignancy.

We detected ME, ADH and DCIS in calcified as well as non-calcified cores and sometimes exclusively in the non-calcified cores. Radiologically therefore it is prudent to obtain sufficient tissue for histological diagnosis rather than complete removal of calcified areas. We also recommend follow up excision of all the cases having mucin extravasation in their cores.

There was a good correlation between quantitative presence of CCL and Atypical cellular changes on core and excisional biopsies. A multidisciplinary approach should therefore be taken for cases presenting with mucin extravasation, Mucocele like lesion and columnar cell changes in breast core biopsies even in absence of obvious cellular atypia.

## Acknowledgements

The authors would like to thank health promotion board, Singapore for assistance in obtaining data from the Breast Screen program. The authors are also grateful to the staff in pathology; Singapore general hospital for providing access to slides and blocks for the study.

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