

Mucocele-like Lesions Diagnosed on Breast Core Biopsy

Assessment of Upgrade Rate and Need for Surgical Excision

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Upon completion of this activity you will be able to:

- describe the histologic features of mucocele-like lesion of the breast.
- describe the characteristic radiologic findings associated with mucocele-like lesions.
- list the circumstances in which a mucocele-like lesion of the breast requires surgical excision.

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Abstract

Mucocele-like lesion (MLL) is a rare mucinous lesion of the breast with highly variable upgrade rates to atypia or malignancy on excision. This spectrum of data has led to differing opinions on the need for surgical excision. We evaluated 50 core biopsy specimens diagnosed as having MLLs and correlated the findings with those of excision pathology. Thirty-eight patients underwent surgical excision and 29 were benign (76%), 4 had atypical ductal hyperplasia (11%), and 5 had ductal carcinoma in situ (13%), with an overall upgrade rate of 13%. However, the risk of upgrade was exclusively associated with the presence of atypia as seen on the needle core biopsy. All 22 MLLs without atypia had benign excisions, while 5 (31%) of the 16 patients with MLLs with atypia were upgraded to ductal carcinoma in situ on excision. No invasive carcinoma was identified. We believe it is reasonable that women with the core biopsy diagnosis of MLL without atypia and no associated mass be offered close clinical follow-up as an alternative to surgery.

A mucocele-like lesion (MLL) is a rare mucinous lesion of the breast first described by Rosen in 1986.¹ An MLL consists of mucin-filled cysts lined by flat or cuboidal epithelium with foci of stromal mucin extravasation. Calcifications are frequently present within the cysts, allowing for mammographic detection.² The pathogenesis of this lesion is not entirely clear, although excess production of mucinous secretions and duct obstruction may be contributing factors.¹ Since the original description, there has been greater recognition of this entity, and subsequent studies of MLL have detailed its association with benign, atypical, and malignant lesions.³⁻⁵ Rates at which MLLs diagnosed on core biopsy are upgraded to atypia or malignancy on excision range from 0% to 43%, and this spectrum of data has led to differing opinions on the need for surgical excision.⁶⁻⁸ The goal of this study was to determine the upgrade rate of MLL at a large tertiary hospital breast cancer center and to potentially identify a specific patient population in which close clinical follow-up may be a reasonable alternative to surgery.

Materials and Methods

After institutional review board approval, the surgical pathology database at Northwestern Memorial Hospital (Chicago, IL) was searched to identify all breast needle core biopsies performed between January 1, 2003, and March 31, 2011, with MLL as one of the final diagnoses or with MLL described in a note. Fifty-eight biopsy samples from 57 patients were identified. All needle core biopsies were performed by radiologists, and the tissue specimens were

fixed and processed routinely. As per the standard microtomy protocol for breast needle core biopsies at our institution, 4 levels cut at 50- μ m intervals were examined for each paraffin-embedded tissue block. Patient data including age at diagnosis, mammographic and ultrasonographic findings, and pathologic diagnosis at excision were recorded. All available core biopsy slides were reviewed by a pathologist with subspecialty training in breast pathology to confirm the presence of an MLL. The location of the calcifications (associated with the MLL or in the background breast tissue) and the number of cores obtained was also noted. All imaging studies were reviewed by radiologists with subspecialty expertise in breast imaging. The MLL core biopsy specimens were then subdivided into categories based on the associated pathology: MLL with ductal carcinoma in situ (DCIS), MLL with ductal epithelial atypia (including flat epithelial atypia and atypical ductal hyperplasia [ADH]), MLL with lobular neoplasia, or MLL with benign breast tissue. All available excision pathology reports were reviewed. For the purposes of this study, an “upgrade” was defined as the presence of DCIS or invasive carcinoma found on excision in a patient in whom prior breast core biopsies showed only either MLL or MLL with atypia.

Results

MLL was diagnosed in 58 (0.2%) of 23,962 breast needle core biopsies performed in the study period. The 57 patients (1 patient had 2 separate needle core biopsy findings of MLL) had a mean age of 54 (range 27-82) years. Fifty-five biopsies were performed using stereotactic guidance targeting calcifications (95%), and 3 biopsies were ultrasound guided targeting a mass (5%). Thirty core biopsy specimens (52%) were diagnosed as benign MLL, 23 (40%) as MLL with atypia (2 with flat epithelial atypia and 21 with ADH), 4 (7%) as MLL with DCIS, and 1 (2%) as MLL with lobular carcinoma in situ.

Slides were available for review in 51 of the core biopsies, of which 49 were stereotactic biopsies targeting microcalcifications. Overall, the MLLs contained microcalcifications in

all but 11 cases (77.6%). There were 5 “incidental” MLLs in which the calcifications were only identified in the surrounding benign breast tissue. Eighty-six percent (24/28) of benign MLLs had calcifications in the mucin. In cases in which the MLL was associated with either ductal epithelial atypia or DCIS, the calcifications were more likely to be found in both lesions rather than purely in the MLL (15/20 or 75% vs 5/20 or 25%). In the one stereotactic biopsy sample with an MLL and lobular carcinoma in situ, the calcifications were in the mucin. In the ultrasound-guided needle core biopsies targeting a mass, calcifications were not present in the MLL.

Surgical and clinical follow-up information was obtained on the 50 patients without known ipsilateral breast cancer (31 benign MLL and 19 MLL with atypia). Thirty-eight patients underwent surgical excision of the MLL at our institution; MLLs with atypia were more likely to undergo immediate excision than those without (22/31 or 71% from the benign MLL group and 16/19 or 84% from the MLL with atypia group). Of the excisions, 29 were benign (76%), 4 had ADH (11%), and 5 had DCIS (13%), for an overall upgrade rate of 13% (Table 1). However, the risk of upgrade was exclusively associated with the presence of atypia in the needle core biopsy or the presence of a mass on imaging; these 2 subsets of patients accounted for all of the upgrades. All 22 MLLs without atypia had benign excisions, while 5 (31%) of the 16 patients with MLL with atypia were upgraded to DCIS on excision. Two patients had a mass associated with their MLL and both underwent excision; one had 0.5 cm of DCIS in her lumpectomy, thus reaching an upgrade rate of 50% in this clinical setting (Image 1). No invasive carcinoma was identified in any of the excisions.

The extent of sampling of the mammographic lesion at the time of biopsy as estimated by the number of cores obtained may also affect the likelihood of upgrade at the time of excision. Overall, an average of 9 cores was obtained per procedure. For the 3 main groups—benign MLL, MLLs with atypia, and MLLs with DCIS—the average number of cores was 8.8, 8.5, and 10.6, respectively. Considering only the MLLs with atypia on core biopsy, the average number of cores for the patients upgraded at excision (9.3) was slightly

Table 1
Excision Results of MLLs Diagnosed on NCB

Imaging and/or NCB Diagnosis	Total	No. Excised	No. of Excisions With DCIS	No. of Excisions With IC	Upgrade Rate, %
MLL with calcifications	47	36	4	0	11*
MLL with mass	3	2	1	0	50
MLL without atypia	31	22	0	0	0
MLL with atypia	19	16	5	0	31

DCIS, ductal carcinoma in situ; IC, invasive carcinoma; MLL, mucoccele-like lesion; NCB, needle core biopsy.

* All MLLs associated with calcifications that were upgraded also had atypia within the NCB.

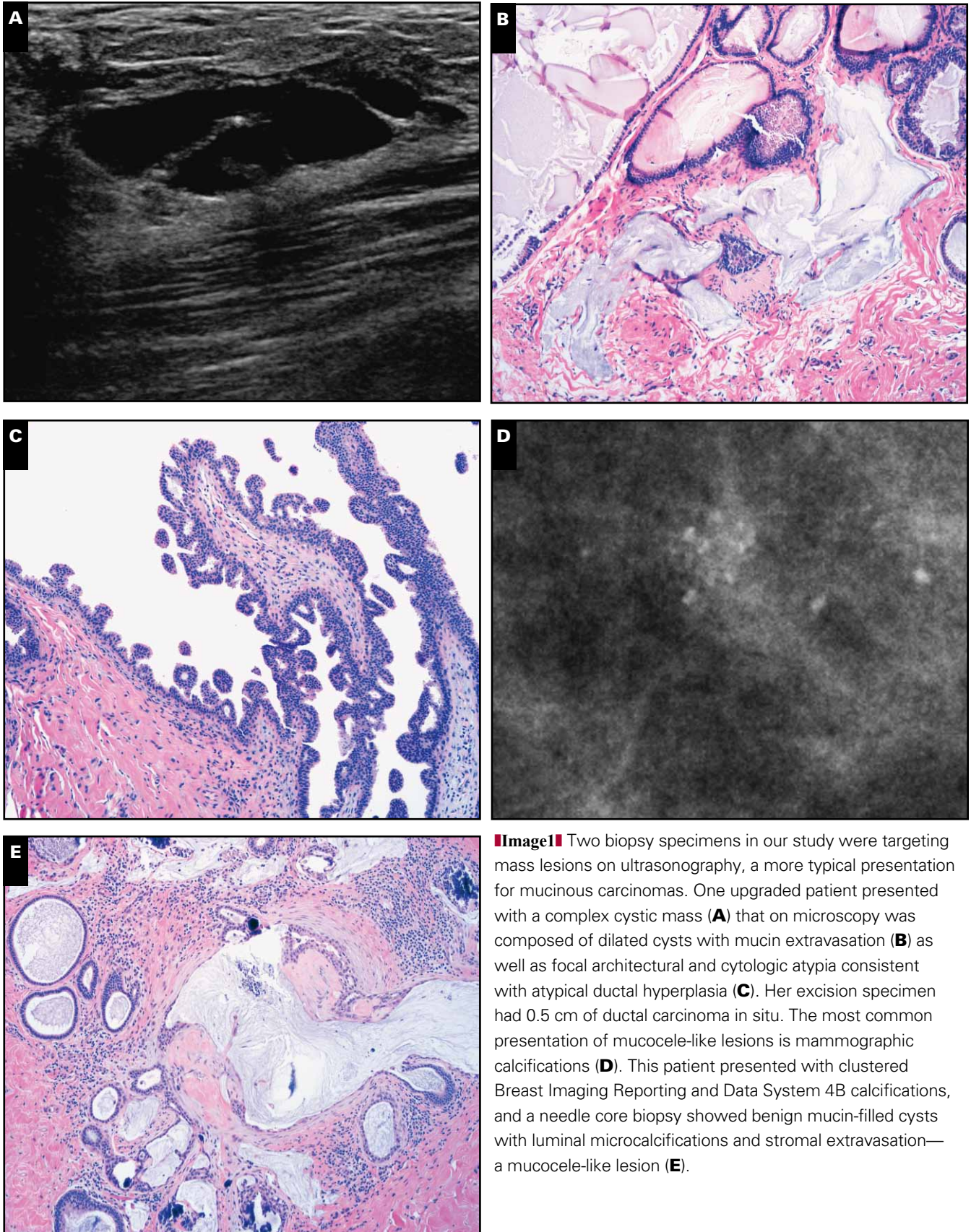


Image 1 Two biopsy specimens in our study were targeting mass lesions on ultrasonography, a more typical presentation for mucinous carcinomas. One upgraded patient presented with a complex cystic mass (**A**) that on microscopy was composed of dilated cysts with mucin extravasation (**B**) as well as focal architectural and cytologic atypia consistent with atypical ductal hyperplasia (**C**). Her excision specimen had 0.5 cm of ductal carcinoma in situ. The most common presentation of mucocele-like lesions is mammographic calcifications (**D**). This patient presented with clustered Breast Imaging Reporting and Data System 4B calcifications, and a needle core biopsy showed benign mucin-filled cysts with luminal microcalcifications and stromal extravasation—a mucocele-like lesion (**E**).

greater than the average number obtained for patients who were not subsequently upgraded (8.9).

Twelve patients did not undergo excision of their MLL at our institution, 3 of whom were unavailable for follow-up. Eight patients with MLL alone on core biopsy returned for subsequent breast imaging, and none have gone on to develop breast cancer (mean follow-up time, 43 mo; range, 22-87 mo). One woman who was found to have both MLL and ADH on core biopsy opted for clinical follow-up rather than surgical excision and has stable mammographic findings 12 months after her diagnosis.

Discussion

Mucinous lesions of the breast are diverse and range from fibrocystic changes with mucin-filled ducts to mucinous carcinoma.⁸⁻¹⁰ Although MLL appears to fall at the benign end of the pathologic spectrum, associations with ADH, DCIS, and invasive carcinoma have been reported. Data on the management of MLL have increased significantly since the original description of this lesion by Rosen in 1986.¹ In their often-cited 2002 article, Jacobs et al¹¹ “strongly advise” that a diagnosis of MLL on needle core biopsy should prompt an excision if it is believed that the core biopsy may be missing mucinous DCIS or invasive mucinous carcinoma. However, at that time, data supporting or refuting such a recommendation were limited. Unfortunately, many subsequent studies have been limited by small numbers and insufficient pathologic-radiologic concordance, leading to conflicting opinions about the management of MLLs diagnosed on needle core biopsy.

Several studies have shown that mucinous lesions can be reliably diagnosed on core biopsy. Renshaw⁶ evaluated 22 core biopsies with mucinous lesions, and on comparing them with 15 corresponding excision specimens, found no changes in diagnosis from benign to malignant or vice versa. Wang et al¹² showed similar findings in their series of 32 core biopsies with corresponding excisions and suggested that MLLs without atypia on core biopsy may not require surgical excision. In a more recent study, Carkaci et al¹³ identified 44 patients with MLL diagnosed either on core biopsy or fine-needle aspiration, 16 of whom underwent surgical excision. Three (19%) of 16 patients were upgraded from ADH on biopsy to DCIS on excision. None of the patients with MLL without atypia had a malignant lesion on excision. The authors subsequently suggested that in the absence of a radiographic mass with irregular margins, an MLL without ADH may not require excision.

A review of these aforementioned articles would appear to point to a consensus on the management of MLLs. However, other authors advocate for the excision of all MLLs

regardless of the presence of atypia. Carder et al¹⁴ evaluated 11 cases of MLL diagnosed on core biopsy, of which 10 patients underwent surgical biopsy. Six cases showed only MLL on biopsy, of which 2 (33%) contained ADH in the excision. Four cases showed MLL with ADH on biopsy and 3 (75%) were malignant on excision (2 micropapillary DCIS and 1 invasive mucinous carcinoma). One case contained only residual MLL with ADH. Given these findings, the authors believed it would be prudent to recommend surgical excision for all MLLs because of the associated risk of finding at least ADH on excision. In a more recent study, Jaffer et al⁷ expressed similar concern regarding MLL and its association with ADH. They evaluated 45 core biopsies containing MLL with corresponding excisions and found that 7 (16%) resulted in ADH and 1 (2%) had DCIS. Although the rate of upgrade to malignancy was very low, the authors emphasized their support for excising benign MLLs because finding ADH will at least inform the patient and clinicians of an overall increased risk of breast cancer and allow for more frequent screening if necessary.

Given these conflicting recommendations based on published data, we attempted to address some of the aforementioned limitations and shed light on this topic with our institutional experience. The 58 MLLs included in our study constitute one of the largest groups in the published literature. Although many studies include ADH when defining an upgrade, we decided to limit upgrades to cases with *in situ* or invasive carcinoma because either of these diagnoses necessitates further intervention that may include additional surgery, endocrine prophylaxis, or chemotherapy. A diagnosis of ADH is not necessarily treated in such a manner, and including it as an “upgrade” could overestimate the risk associated with MLL. All available core biopsy slides and pertinent imaging studies were reviewed by physicians with subspecialty expertise in breast pathology and radiology. We thus ensured strict pathologic-radiologic concordance to better exclude lesions in which a discordant needle core biopsy diagnosis would trigger additional tissue sampling (either rebiopsy or excision). Without evaluating for concordance, cases like these are erroneously considered an “upgrade.”

The demographic and imaging characteristics of patients diagnosed with MLL during a more-than-8-year period at our institution are largely consistent with other studies. Women with MLL were typically middle aged, although the age range was wide (27-82 years). Almost all of the MLLs were detected because of calcifications, with only 3 appearing as a mass. Microscopically identified calcifications were present in the MLL itself in 78% of cases. When considering all the patients included in our study, the overall upgrade rate was 13%, but this number does not tell the entire story. When the MLL group is divided into those with and without adjacent ductal epithelial atypia in the same core biopsy,

2 distinct groups emerge. For MLLs without atypia, the upgrade rate was 0%, whereas for those with atypia it was 31%. This 0% upgrade rate for MLLs without atypia is in keeping with several other aforementioned studies (Table 2).

Most MLLs are clinically occult and manifest as clustered, indeterminate calcifications on mammography; their number and morphology do not necessarily distinguish benign from malignant.^{2,8} However, the presence of a mass, particularly with ill-defined or irregular borders, is worrisome and not necessarily explained by the presence of an MLL on core biopsy.¹³ Begum et al¹⁵ evaluated 39 mucinous lesions and identified 1 case with acellular mucin pools on core biopsy that were ultimately found to be a component of a mucinous carcinoma on excision. However, the authors note that the diagnosis of acellular mucin was discordant with the imaging findings of a symptomatic mass. Although this presentation is uncommon, there was a 50% chance of upgrade for mass-associated MLLs in our study. Based on this, we continue to recommend surgical excision in this subset of patients.

It bears mentioning that several studies have raised concerns about potential sampling error affecting the diagnosis of mucinous breast lesions given their cellular heterogeneity, particularly in mucinous carcinoma.^{14,15} To help address the sampling question, we looked at the number of cores obtained during the biopsy procedure. Significantly, there was no marked difference in the average number of cores when comparing the different MLL groups. As would be expected, a slightly higher average number of cores were obtained in cases that could be categorized as MLL and DCIS on core biopsy alone compared with the atypical MLL group (10.6 vs 8.5). When considering only the atypical group, however, virtually no difference was found between the number of cores obtained from the upgraded patients and those not upgraded, showing that sampling likely did not significantly affect the upgrade rate.

A mammographic finding of a small cluster of indeterminate calcifications is quite different from a large span of

pleomorphic calcifications; however, at the time of sign-out the pathologist often does not know the particular details of the imaging findings. The one upgrade noted by Jaffer et al⁷ was targeting widespread suspicious calcifications, and the core biopsy showed only an MLL with atypical lobular hyperplasia. Because neither lesion likely explains the calcifications described in this patient, these results should be considered discordant. This case illustrates how careful communication between the pathologist and radiologist is paramount when deciding on concordance for MLLs. Although the potential for underdiagnosis of mucinous carcinoma on core biopsy exists, we found no cases with invasive carcinoma in the excision specimen, mucinous or otherwise. Therefore we believe that through careful pathologic-radiologic concordance, this risk can be minimized while at the same time saving many patients an unnecessary trip to the operating room.

In conclusion, our series is one of the largest to date of its kind and adds to the growing body of data regarding MLLs. Our results showed no upgrades at excision for MLLs without adjacent ADH in the core biopsy and a 31% upgrade rate for MLLs with ADH. These findings corroborate those of other studies that also demonstrated 0% upgrade rates to malignancy in the absence of initial atypia on core biopsy. Also, no women in our data set who opted to forego surgical excision of their MLL have gone on to develop breast cancer in a mean follow-up period of almost 4 years. However, the risk of upgrade is significantly higher when the MLL is associated with a mass, regardless of associated atypia. Given the 50% upgrade rate, all mass-associated MLLs should be excised because a more significant lesion cannot be comfortably excluded based on core biopsy sampling alone. When dealing with calcifications, the determination of pathologic-radiologic concordance is critical. If concordant, we believe it is reasonable that women with the core biopsy diagnosis of MLL without atypia and no associated mass be offered close clinical follow-up as an alternative to surgical excision.

Table 2
A Review of the Literature on Mucocele-like Lesions

Reference	No. of MLL NCB Without Atypia	No. Excised	DCIS or IC Present on Excision	Upgrade Rate, %
Renshaw ⁶	5	3	0	0
Carder et al ¹⁴	7	6	0	0
Ramsaroop et al ⁸	9	9	2	22
Wang et al ¹²	6	6	0	0
Begum et al ¹⁵	21	9	0*	0
Carkaci et al ¹³	22	7	0	0
Jaffer et al ⁷	61	45	1	2

DCIS, ductal carcinoma in situ; IC, invasive carcinoma; MLL, mucocele-like lesion; NCB, needle core biopsy.

* One core biopsy contained only acellular mucin pools and was discordant with imaging findings of a mass; therefore, the finding of mucinous carcinoma on excision may not represent a true upgrade.

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