Published in final edited form as:

Hum Pathol. 2016 March ; 49: 33–38. doi:10.1016/j.humpath.2015.10.004.

Mucocele-Like Lesions of the Breast: Clinical Outcome and Histological Analysis of 102 Cases

Annie L. Meares, MD^a, Ryan D. Frank, BA^b, Amy C. Degnim, MD^c, Robert A. Vierkant, MS^b, Marlene H. Frost, PhD^d, Lynn C. Hartmann, MD^d, Stacey J. Winham, PhD^b, and Daniel W. Visscher, MD^a

^aDivision of Anatomic Pathology, Mayo Clinic, Rochester, MN

^bDivision of Biomedical Statistics and Informatics, Mayo Clinic, Rochester, MN

^cDepartment of Surgery, Mayo Clinic, Rochester, MN

^dDepartment of Medical Oncology, Mayo Clinic, Rochester MN

Abstract

Mucocele-like lesions (MLL) of the breast are characterized by cystic architecture with stromal mucin and frequent atypia, but it is unknown whether they convey long term breast cancer risk. We evaluated 102 MLL that were derived from a single institution benign breast disease (BBD) cohort of 13412 women who underwent biopsy from 1967–2001. MLL were histologically characterized by type of lining epithelium, architecture of the lesion, associated atypical hyperplasia (AH) and for incidence of breast cancer (14.8 years median follow-up). A relatively large proportion of MLL (42%) were diagnosed in women >55 years of age. AH was significantly more frequent in MLL patient compared to the cohort overall (27% vs 5%, $p < 0.001$). Breast cancer has developed in 13 patients with MLL. This frequency is only slightly higher than population expected rates overall (Standardized incidence ratio (SIR) 2.28, 95% CI 1.21–3.91), and not significantly different from women in the cohort with (non atypical) proliferative breast lesions. Younger women (<45) with MLL had a non-significant increase in risk of cancer compared to the general population (SIR 5.16, 95% CI 1.41–13.23). We conclude MLL is an uncommon breast lesion that is often associated with co-existing AH. However, in women over age 45, MLL do not convey additional risk of breast cancer beyond that associated with the presence of proliferative disease.

Keywords

Breast carcinoma; benign breast disease; fibrocystic breast disease; atypical hyperplasia; mucocele-like lesion; columnar cell change

Address Correspondence to: Daniel W. Visscher, M.D., Mayo Clinic, Division of Anatomic Pathology, Hilton 11, 200 First Street, SW, Rochester, MN 55905, Phone 507-538-3205, FAX 507-284-1599, visscher.daniel@mayo.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Conflict of Interest Statement: The authors declare that they have no financial or nonfinancial relationships to disclose.

1.1 Introduction

Mucocele like lesions (MLL) of the breast were initially described by Rosen et al[1–2]. The name reflects histologic analogy to an important feature of minor salivary gland lesions, namely the presence of extravasated acellular mucin in periductal stroma. MLL in the breast are characterized by a multilocular cystic character. The reason for mucin extravasation is unclear but it is not thought to derive from mechanical duct obstruction. Although there is variable associated hyperplasia of the cyst lining in MLL, there are no epithelial cells “floating” within the luminal or extravasated mucin (i.e., apart from artifacts associated with tissue sectioning or displaced cells from prior needle core biopsy). This negative microscopic finding is critical in distinguishing MLL from mucinous carcinomas of the breast.

A number of reports have subsequently described an association between MLL and the simultaneous presence of atypical ductal hyperplasia (ADH), ductal carcinoma in situ (DCIS), and/or mucinous carcinomas[3–8]. The frequency of ADH associated with MLL reported in the literature ranges from 11–57%, and that of DCIS from 2–30%[3–8]. This finding has prompted some to consider MLL as a precursor to breast cancer. Accordingly, MLL encountered on needle core biopsies are considered “high-risk” and excisional biopsy is recommended in order to rule out malignancy.

To date, no study has evaluated long term breast cancer risk in a series of patients with MLL diagnosed in an otherwise benign biopsy. The lack of literature in this area reflects the difficulty in collecting a significant number of these uncommon cases; they comprise <1% of diagnoses in benign breast biopsies. The objective of our study was to collect and perform a retrospective analysis of MLL in a large benign breast disease cohort. Our goal was to define the histologic features in a series of non-selected cases and to determine whether MLL are associated with increased breast cancer incidence in follow-up.

1.2 Materials and Methods

1.2.1 Study population and histopathologic review

MLL cases were derived from the Mayo Benign Breast Disease Cohort which includes 13,412 women who underwent a benign breast biopsy during the years 1967–2001 at the Mayo Clinic, Rochester, Minnesota. Original slides from all cases were retrospectively reviewed in a blinded manner by a single pathologist (DWV). Fibrocystic lesions of all types, including MLL, were recorded as present or absent in each biopsy and biopsies were placed into overall classification categories as non proliferative, proliferative and atypical hyperplasia (i.e. atypical ductal or atypical lobular). Samples with MLL were re-reviewed histologically and classified by type of lining (flat/attenuated, simple columnar, columnar hyperplasia, usual duct hyperplasia, atypical hyperplasia) and extent/architecture (i.e. unifocal vs multifocal).

1.2.2 Follow-up data

Follow-up for post benign biopsy breast cancer events and demographic data were obtained through Mayo medical records and a study questionnaire. All protocol procedures and

patient contact materials were reviewed and approved by the Institutional Review Board (IRB) of the Mayo Clinic. Patients were not included if Research Authorization was refused.

1.2.3 Statistical analysis

Data were summarized descriptively using frequencies and percents for categorical variables and medians and interquartile ranges (IQRs) for continuous variables. We compared distributions of demographic and clinic characteristics across levels of MLL status using chisquare tests of significance.

The length of follow-up for each woman in the study was defined as the number of days from her benign biopsy to the date of her breast cancer diagnosis, death, or last contact. Additional censoring events for follow-up included prophylactic mastectomy and diagnosis of lobular carcinoma in situ (LCIS). We estimated relative risks, overall, and by levels of MLL, age at diagnosis and initial histologic impression, with standardized incidence ratios (SIRs) by dividing the observed number of incident breast cancer events by population-based expected values. Rates of breast cancer development could thus be compared with that of the general population rather than an internal reference group, recognizing that our cohort was at overall increased risk for development of breast cancer by virtue of having a benign biopsy. Expected SIRs were calculated by apportioning each woman's person-years of follow-up into five-year age and calendar period categories and multiplying these by the corresponding breast cancer incidence rates from the Iowa Surveillance, Epidemiology, and End Results (SEER) registry. Tests for heterogeneity in SIRs across levels of MLL status were carried out using a Poisson regression analysis that accounted for the population based expected event rate for each individual using an offset term. All statistical sets were two-sided, and all analyses were conducted using the SAS version 9.3(SAS Institute, Inc., Cary, NC) software system. A p-value of 0.05 was determined to be significant.

1.3 Results

1.3.1 Demographic Features

A total of 102 subjects with MLL were identified in our cohort. Demographic and clinical characteristics of these individuals are summarized in Table 1. There were no statistically significant differences in the age distribution at time of benign breast biopsy in the patients with MLL compared to those without MLL. There were significant differences in age and year of biopsy between those with and without MLL. MLL women tended to be older and more likely to be from the mammographic era, with p-values of 0.0001 and 0.012, respectively.

1.3.2 Histologic Features

MLL were characterized by multilocular cystic structures, some of which filled the entire microscopic fields at scanning magnification (Figure 1). The cystic structures were distended with acellular, faintly basophilic mucin. By definition, the mucin dissected at least focally into surrounding stroma, but the mucin extravasation was often quite inconspicuous. Intraluminal calcifications, often large and coarse with a fragmented "debris-like" appearance, were associated with many cases (Figure 2).

In virtually all cases, MLL occurred in association with or at the edge of a columnar altered lobule. Accordingly, at least part of the MLL was lined by columnar epithelium. Most lesions were comprised of multiple crowded locules; whereas the larger cystic structures often had an attenuated epithelial lining, smaller locules generally showed a combination of simple columnar and hyperplastic columnar epithelium (Figure 3). The majority of cases (n=91) had a combination of different types of epithelium; four cases had only attenuated lining, 3 had only simple columnar, and 4 had only hyperplastic columnar epithelium. The cells in these proliferative areas appeared hyperchromatic, in part owing to a high amount of nuclear overlap. In some lesions, the lining had a papillary hyperplastic appearance.

MLL showed variable architecture and distribution. While most lesions were characterized by a discrete group of cystic structures, what we termed “classic” type MLL, others displayed a more diffuse distribution, or “variant” MLL (Figure 4). Of the more diffuse cases, one type resembled cystic mastopathy, with multiple back-to-back cyst-like structures occupying the entire biopsy specimen. Others exhibited multiple cystic structures surrounded by a host response, characterized by periductular fibrosis and a chronic inflammatory infiltrate, so-called duct ectasia-like MLL. The majority of cases (64/102) were “classic” type MLL. Of the remainder “variant” cases (38/102), 20 were cystic-mastopathy-like, 11 were duct ectasia-like, and 7 had features of both duct ectasia and cystic mastopathy.

Atypical lesions were associated with some MLL. A proportion of MLL were lined by cells with low grade cytologic atypia, but lacking classic monotypic cytology, loss of polarity and layering of flat epithelial atypia (FEA). Other cases additionally showed rigid architectural formations fulfilling criteria for ADH (Figure 5). In 6, the ADH was present exclusively inside of the MLL, in 7 it was located outside of the MLL and in 11 the ADH was present both in and outside the MLL. Atypical lobular hyperplasia (ALH) was identified in 8 cases (all but one located away from the MLL).

Based on degree of epithelial hyperplasia, most MLL were classified as proliferative or atypical (52% and 27%, respectively). This distribution of overall histologic classification was significantly different from women in the cohort without MLL (see Table 1), in which 32% were proliferative and 5% were atypical. The atypia was ADH in 71%, ALH in 14%, and both ADH and ALH in 14%. Flat epithelial atypia (FEA), not included in the original category of “atypias” was identified in 9% of MLL cases. The atypia was often not present in the MLL itself but observed in surrounding tissue. In MLL samples with ADH, the atypia was located outside the lesion in 6 of 23 (26%) cases. In samples with ALH, 7 of 8 (88%) were located outside the MLL. The high frequency of associated proliferative lesions in part reflects the background of MLL lesions, which often had a “busy” appearance with multiple columnar altered lobules, adenosis, and usual ductal hyperplasia.

1.3.3 Outcome of MLL

Overall, thirteen patients with MLL have developed breast cancer in follow-up (3 of 22 with nonproliferative histology, 6 of 53 with proliferative histology, and 4 of 27 with atypia). The median time to cancer was 11.8 years (range 0.7 to 31.1). Forty-six percent of cancers were subsequently diagnosed in the contralateral breast to the benign biopsy. Nine carcinomas

were invasive and 4 were in-situ. Of the invasive cancers, 6 were ductal, 2 were lobular, and 1 was mixed; none of these were mucinous carcinomas. Of the in-situ cancers, all were DCIS. The majority of patients who developed cancer had “classic” MLL architecture (12 of 13) with hyperplastic columnar epithelium (11 of 13).

Overall, women with MLL seemed to have slightly higher risk of subsequent breast cancer (SIR 2.28, 95% CI 1.21–3.91) than those without MLL (SIR 1.63, 95% CI 1.54–1.73, Table 2), but this comparison was not significant (p-value 0.255). In addition, when examining associations within subgroups of histologic impression, this apparent difference attenuated (Table 2Figure 6). Women with MLL diagnosed before the age of 45 were perhaps at higher risk of subsequent breast cancer (SIR 5.16, 95% CI 1.41–13.23) than women of similar age and no MLL (SIR 1.80, 95% CI 1.62–2.01), but this difference was not statistically significant (test for heterogeneity $p=0.07$) due in large part to the small number of cancer events in the MLL group.

1.4 Discussion

This is the first study to systematically collect a series of MLL and review their outcome. The literature, apart from case reports with pathologic descriptions with radiologic correlation and needle core biopsy “upgrade” studies based on a small number of cases, reveals virtually nothing about the long-term breast cancer risk attributable to benign MLL. Based on our data, we conclude that MLL of the breast are uncommon lesions that likely represent a variant or dramatic manifestation of columnar cell alteration. Although MLL are commonly associated with atypical hyperplasias, our data demonstrate that MLL do not confer significantly elevated breast cancer risk (Figure 6). Only 13% of MLL in this series developed breast cancer in followup (a number similar to that of the cohort overall) and only 4 of 27 MLL with concurrent atypia has developed breast carcinoma to date. We theorize the reason we may not be observing the expected risk is that MLL tend to occur in older aged patients in whom atypical/proliferative lesions are intrinsically lower risk (8).

We emphasize, however, that there are insufficient numbers of MLL cases in this cohort to detect subtle or age specific associations with increased risk. Our data could be interpreted as showing that there is not necessarily a dramatic breast cancer risk or association (i.e. one that could be identified with a relatively small number of cases), other than that associated with proliferative histology. The exception would be in women less than 45 years, which may represent a high risk subset.

MLL appear to be a morphologically heterogeneous entity with differences in type of epithelium as well as architecture and distribution. The present inclusive definition could potentially identify other conditions which may be multifocal such as cystic mastopathy or duct ectasia. These other conditions may possess a different biology than MLL and may produce radiologic-pathologic discordance.

Although MLL was a rare diagnosis in this cohort, accounting for less than 1% of cases reviewed, the relative incidence may be higher in more recent surgical material. This higher incidence reflects the increasing use of screening mammography, which was not prevalent

until the second half of this cohort group. Virtually all MLL are associated with prominent microcalcifications, which are often conspicuous on mammography. Hence, the incidence of MLL is likely increasing in surgical pathology material as partly shown by the appearance of greater numbers of MLL in the latter years of the cohort.

The differential diagnosis of MLL includes colloid or mucinous carcinoma. In contrast to MLL, mucinous carcinomas are characterized by a prominent luminal cell proliferation, although they may have a cystic character. Mucinous carcinomas also demonstrate variable number of tumor cells along with fibrocytes and vessels “floating” within luminal mucin. It is emphasized that in MLL, the luminal mucin is, by definition, devoid of (non-displaced) epithelial cells. Other differential diagnoses include cystic mastopathy and florid duct ectasia with luminal mucin. The former lesion is generally associated with prominent apocrine differentiation, in contrast to the epithelium in MLL, which has a columnar appearance. Florid duct ectasia generally contains lipid-rich material within ducts with prominent foamy histiocytes, in contrast to the acellular luminal mucous seen in MLL.

Our study should be interpreted cautiously in view of several limitations. First, since MLL cases were derived from benign breast biopsies, we were not able to evaluate the presence of associated DCIS, as has been described in the literature. It is possible that the MLL we evaluated represent an indolent subset within the MLL spectrum. Second, a proportion of our cases were from the non-mammographic era where excisions were performed for palpable lesions, as opposed to radiographic findings, such as calcifications. Caution should be taken in extrapolating the outcome data to the current practice setting where many lesions, perhaps the majority, are detected radiographically. Finally, this study does not address whether MLL on needle core biopsy requires excision, due to small numbers of women who had MLL on core biopsies (N=12). We concur with others who recommend consideration of excision of MLL when they are encountered on needle core breast biopsies, especially in light of the fact that atypical hyperplasia is frequently encountered adjacent to the MLL. However, clinical and radiographic factors need to be taken into account in management of patients with MLL in small biopsy samples.

1.5 Conclusion

Our study confirms the observation of others that MLL are associated with a highly elevated likelihood for synchronous atypical hyperplasia (27% in MLL patients versus 5% in the cohort overall). We have shown that the associated risk of MLL, however, does not approach that of atypical hyperplasias in general, but is lower and more similar to proliferative disease without atypia. The reasons for MLL’s association with atypia are unclear; however, we theorize that a mucinous secreting phenotype is a variant of columnar cell change and therefore has a risk level similar to proliferative disease. We recommend careful evaluation of MLL when encountered in biopsy materials in order to exclude concurrent atypical hyperplasia.

Acknowledgments

Funding support: Supported by the Mayo Clinic Breast Cancer Specialized Program of Research Excellence (SPORE) grant p50CA116201 from the NIH (to Drs Hartmann and Visscher), the Susan B. Komen Foundation

grant KG110542 (to Dr Hartmann), and the National Cancer Institute (grant NCI R01 CA132879 to Dr Hartmann). The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

References

1. Rosen PP. Mucocoele-Like Tumors of the Breast. *Am J Surg Pathol.* 1986; 10:464–469. [PubMed: 3014913]
2. HameleBena D, Cranor ML, Rosen PP. Mammary mucocoele-like lesions - Benign and malignant. *Am J Surg Pathol.* 1996; 20:1081–1085. [PubMed: 8764744]
3. Jaffer S, Bleiweiss IJ, Nagi CS. Benign mucocoele-like lesions of the breast: revisited. *Mod Pathol.* 2011; 24:683–687. [PubMed: 21240257]
4. Ohi Y, Umekita Y, Rai Y, Sagara Y, Baba S, Tamada S, Kukita T, Yoshioka T, Hatanaka K, Tanimoto A. Mucocoele-like lesions of the breast: a long-term follow-up study. *Diagn Pathol.* 2011; 6:29. [PubMed: 21466711]
5. Rakha EA, Shaaban AM, Haider SA, Jenkins J, Menon S, Johnson C, Yamaguchi R, Murphy A, Liston J, Cornford E, Hamilton L, James J, Ellis IO, Lee AH. Outcome of pure mucocoele-like lesions diagnosed on breast core biopsy. *Histopathology.* 2013; 62:894–898. [PubMed: 23402386]
6. Ro JY, Sneige N, Sahin AA, Silva EG, del Junco GW, Ayala AG. Mucocoelelike tumor of the breast associated with atypical ductal hyperplasia or mucinous carcinoma. A clinicopathologic study of seven cases. *Arch Pathol Lab Med.* 1991; 115:137–140. [PubMed: 1847035]
7. Sutton B, Davion S, Feldman M, Siziopikou K, Mendelson E, Sullivan M. Mucocoele-like lesions diagnosed on breast core biopsy: assessment of upgrade rate and need for surgical excision. *Am J Clin Pathol.* 2012; 138:783–788. [PubMed: 23161710]
8. Hartmann LC, Sellers TA, Frost MH, Lingle WL, Degnim AC, Ghosh K, Vierkant RA, Maloney SD, Pankratz VS, Hillman DW, Suman VJ, Johnson J, Blake C, Tlsty T, Vachon CM, Melton LJ 3rd, Visscher DW. Benign breast disease and the risk of breast cancer. *N Engl J Med.* 2005; 353:229–237. [PubMed: 16034008]

Figure 1.
Numerous cystic structures containing mucinous material (H&E, 4x)

Figure 2.
Extravasated mucin present within the stroma, associated with coarse fractured calcifications
(H&E, 10x)

Figure 3.
Histologic spectrum of cyst lining in MLL A)MLL with attenuated epithelium B) MLL with simple columnar epithelium and adjacent mucin extravasation with associated calcifications C)MLL with hyperplastic columnar epithelium (H&E, 20x)

Figure 4.
Variant MLL-A) Multiple back to back cysts involving the entire specimen, so called “cystic mastopathy-like MLL B) Duct ectasia -like MLL with periductal fibrosis and chronic inflammatory infiltrate (H&E, 4x)

Figure 5.
Atypical ductal hyperplasia involving a MLL with abundant extravasated mucin (H&E, 10x)

Figure 6.
Cumulative incidence of breast cancer by MLL status and histologic impression

Table 1

Distributions of demographic and clinic characteristics across MLL status

Characteristic	No MLL (N=13310)	MLL (N=102)	p-value ^a
Breast Cancer Status			0.248
Control	12060 (90.6%)	89 (87.3%)	
Case	1250 (9.4%)	13 (12.7%)	
Age of BBD			0.001
<45	4358 (32.7%)	17 (16.7%)	
45–55	3888 (29.2%)	42 (41.2%)	
55+	5064 (38.0%)	43 (42.2%)	
Year of Biopsy			0.012
1967–1981	4307 (32.4%)	19 (18.6%)	
1982–1991	4654 (35.0%)	42 (41.2%)	
1992–2001	4349 (32.7%)	41 (40.2%)	
Overall impression			<0.001
NP	8427 (63.3%)	22 (21.6%)	
PDWA	4214 (31.7%)	53 (52.0%)	
AH	669 (5.0%)	27 (26.5%)	

NP, non-proliferative disease; PDWA, proliferative disease without atypia; AH, atypical hyperplasia; MLL, mucocoele like lesion; BBD, benign breast disease cohort

^aChi-square test of significance

Table 2

Associations with breast cancer risk, by levels of MLL, histologic impression, and age

Characteristic	MLL Absent			MLL Present			p-value
	No. Women	Observed Events	Expected Events	No. Women	Observed Events	Expected Events	
Overall	13310	1250	765.66	102	13	5.70	0.255
Age of BBD							
<45	4358	338	187.48	17	4	0.77	0.074
45–55	3888	448	264.55	42	6	2.22	0.292
55+	5064	464	313.63	43	3	2.70	0.604
Overall impression							
NP	8427	619	481.38	22	3	1.14	0.269
PDWA	4214	487	250.77	53	6	3.18	0.943
AH	669	144	33.51	27	4	1.37	0.413

Standardized incidence ratios and corresponding 95% confidence intervals, comparing the observed number of breast cancer events to those expected based on incidence rates from Iowa SEER data. Analyses account for the effects of age and calendar period.