Human Pathology (2016) **49**, 33–38

ELSEVIER

Human PATHOLOGY

www.elsevier.com/locate/humpath

Original contribution

Mucocele-like lesions of the breast: a clinical outcome and histologic 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], Daniel W. Visscher MD[a,*]

[a]*Division of Anatomic Pathology, Mayo Clinic, Rochester, MN 55905*
[b]*Division of Biomedical Statistics and Informatics, Mayo Clinic, Rochester, MN 55905*
[c]*Department of Surgery, Mayo Clinic, Rochester, MN 55905*
[d]*Department of Medical Oncology, Mayo Clinic, Rochester, MN 55905*

Received 26 June 2015; revised 5 October 2015; accepted 8 October 2015

Keywords:
Breast carcinoma;
Benign breast disease;
Fibrocystic breast disease;
Atypical hyperplasia;
Mucoele-like lesion;
Columnar cell change

Summary Mucocele-like lesions (MLLs) 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 MLLs that were derived from a single-institution benign breast disease cohort of 13 412 women who underwent biopsy from 1967 to 2001. MLLs were histologically characterized by type of lining epithelium, architecture of the lesion, associated atypical hyperplasia (AH), and incidence of breast cancer (14.8-year median follow-up). A relatively large proportion of MLLs (42%) were diagnosed in women older than 55 years. AH was significantly more frequent in MLL patient compared to the cohort overall (27% versus 5%; $P < .001$). Breast cancer has developed in 13 patients with MLL. This frequency is only slightly higher than population expected rates overall (standardized incidence ratio, 2.28; 95% confidence interval, 1.21-3.91) and not significantly different from women in the cohort with (nonatypical) proliferative breast lesions. Younger women (<45) with MLL had a nonsignificant increase in risk of cancer compared to the general population (standardized incidence ratio, 5.16; 95% confidence interval, 1.41-13.23). We conclude that MLL is an uncommon breast lesion that is often associated with coexisting AH. However, in women older than 45 years, MLLs do not convey additional risk of breast cancer beyond that associated with the presence of proliferative disease.

☆ Competing interests: The authors declare that they have no financial or nonfinancial relationships to disclose.
☆☆ Funding/Support: Supported by the Mayo Clinic Breast Cancer Specialized Program of Research Excellence grant p50CA116201 from the National Institutes of Health (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 National Institutes of Health.
* Corresponding author. Division of Anatomic Pathology, Mayo Clinic, Hilton 11, 200 First Street, SW, Rochester, MN 55905.
E-mail address: visscher.daniel@mayo.edu (D. W. Visscher).

http://dx.doi.org/10.1016/j.humpath.2015.10.004
0046-8177/

1. Introduction

Mucocele-like lesions (MLLs) 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. MLLs 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 (ie, 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% to 57%; and that of DCIS, from 2% to 30% [3-8]. This finding has prompted some to consider MLL as a precursor to breast cancer. Accordingly, MLLs encountered on needle core biopsies are considered "high risk," and excisional biopsy is recommended 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 less than 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 nonselected cases and to determine whether MLLs are associated with increased breast cancer incidence in follow-up.

2. Materials and methods

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 to 2001 at the Mayo Clinic, Rochester, Minnesota. Original slides from all cases were retrospectively reviewed in a blinded manner by a single pathologist (D. W. V.). 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 nonproliferative, proliferative, and atypical hyperplasia (ie, 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 [AH]) and extent/architecture (ie, unifocal versus multifocal).

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 of the Mayo Clinic. Patients were not included if research authorization was refused.

2.3. Statistical analysis

Data were summarized descriptively using frequencies and percentages for categorical variables and medians and interquartile ranges for continuous variables. We compared distributions of demographic and clinic characteristics across levels of MLL status using χ^2 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. 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 5-year age and calendar period categories and multiplying these by the corresponding breast cancer incidence rates from the Iowa Surveillance, Epidemiology, and End Results 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 tests were 2 sided, and all analyses were conducted using the SAS version 9.3 (SAS Institute, Cary, NC) software system. $P = .05$ was determined to be significant.

3. Results

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