The Hot Topic for today is a biopsy from a 58-year-old woman who had worrisome mammographic microcalcifications on screening.
My name is Dan Visscher; I am a consultant in the Division of Anatomic Pathology at Mayo Clinic Rochester.
Mammographic Microcalcifications: A 58-year-old woman with worrisome mammographic microcalcifications.

Disclosures

• None

I do not have any financial disclosures.
Mammographic Microcalcifications: A 58-year-old woman with worrisome mammographic microcalcifications.

**Utilization Message**

- As you view this presentation, consider the following important points regarding testing:
  - How is the testing going to be used in your practice?
  - When should the tests be used?
  - How will results impact patient management?
So here is our patient's biopsy. As you can see, the tissue shows cystic structures throughout. This is a low-magnification view, so the span of the lesion is at least 5 mm. In addition, we can see mucinous substance, acellular in nature, both within the cysts and in the surrounding stroma where you see the black ink dot.
At higher magnification, we can confirm that the mucin is acellular and that the cysts are lined by an epithelium that is columnar in nature and crowded.
This is a mucocele-like lesion of the breast. They used to be called mucocele-like tumors, and were first described in 1986 by Rosen, owing to its analogy to minor salivary lesions. The most prominent path features include a multilocular cystic character that is accompanied, by definition, with mucin extravasation into stroma; but importantly, we don’t see any cells floating in the mucin as we would in colloid carcinoma. They are associated with a variety of proliferative lesions, in particular, columnar hyperplasia, and they are associated with prominent microcalcifications, accounting for their detection on screening mammography. Often, these are “debris-like” or large.
I did not show you the microcalcifications in the first slide, so here they are. On the bottom panel, we can see a very large microcalcification in the cyst as well as on the upper right panel where there is a large debris-like calcification. Notice the presence of mucin within stroma that is lacking an epithelial lining, and notice also that this mucin is acellular.
Here is another one of these fractured debris-like microcalcifications. The top cyst shows columnar epithelium, and we can see extravasated mucin dissecting collagenous stroma.
Finally, here we see very prominent microcalcifications along with the cystic character of this lesion along with, on the lower left, prominent columnar alteration.
The epithelium in these mucocele-like lesions is typically variable. So in addition to the extravasated mucus above, we see a cyst on the left with simple columnar alteration and a cyst on the lower right that I think lacks polarization and has prominent nuclei that I would characterize as flat atypia.
And indeed, the association between mucocele-like lesions and atypia was described by Ro in 1991, who noted that they can be associated not only with colloid carcinoma but with atypical ductal hyperplasia as well. Other studies have noted that DCIS may be associated with “extraductal” mucin pools. So these studies, as well as the morphology, raised the question that I would like to consider for the balance of the talk, which is whether mucocele-like lesions should be considered a high-risk lesion; and in particular, should they be excised after diagnosis on a needle core biopsy?
And to do that, I would like to review the experience of the Mayo Benign Breast Disease Cohort. This is a group of over 13,000 women that started in the mid-60s who we have been following for over 25 years now in which we have looked at cancer incidence over time. And we can see from this panel that out of about 13,000 women in this cohort, 102 were found to have mucocele-like lesions on re-review of their biopsies. If you look at the age distribution of these lesions, it is different than the BBD cohort overall. In particular, the women with mucocele-like lesions, as seen in this case, are significantly older than the cohort. Notice that 42% of them were over 55 years of age, which is different than typical benign breast disease, which is usually in the 45- to 55-year-old age group.
In the Mayo Benign Breast Disease Cohort, we looked specifically at the kinds of epithelium that were present. Notice on the middle column that most patients had a combination of attenuated, simple columnar, and hyperplastic columnar epithelium; 91 of 103 patients had that combination. Notice also that about 26% of mucocele-like lesions, a similar proportion as reported by Ro, had atypia; that could either have been atypical ductal hyperplasia, atypical lobular hyperplasia, or both. This is significantly higher than the Mayo Benign Breast Disease Cohort overall, which had an overall atypia incidence of about 5%.

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<tr>
<th>Epithelium</th>
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<tr>
<td>Attenuated</td>
<td>4</td>
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<tr>
<td>Simple columnar</td>
<td>3</td>
<td>1</td>
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<tr>
<td>Hyperplastic columnar*</td>
<td>4</td>
<td>3</td>
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<td>Combination</td>
<td>91</td>
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*NOTE: 26% of MLL had atypia (ADH, ALH or both) vs 5% of overall Mayo BBD cohort
Here is an example of one of the hyperplastic lesions we see in mucocele-like lesions. You see the calcifications on the upper right. Notice that there is a pseudocribiform-like proliferation in the middle, which raises the differential diagnosis of atypical ductal hyperplasia.
Here is another case in which we see atypical ductal hyperplasia, both on the far left as well as the upper right. Notice the acellular mucin and higher magnification demonstrates the prototypical cribriform-like arrangement and evenly spaced hyperchromatic monotonous nuclei of atypical ductal hyperplasia along with and associated with microcalcifications.
Our particular patient in this case demonstrated a focus like this one in which we have finger-like projections of cells emanating from flat atypia that I would have characterized as atypical ductal hyperplasia.
So what are the types and distribution of atypia in mucocele-like lesions? Notice that in the atypical ductal hyperplasias, they can be present both inside the lesion as well as in the surrounding tissue or present in both. So in these patients, it is possible not to have the ADH inside the lesion. On the other hand, of patients with atypical lobular hyperplasia, generally the lesion is present outside of the like lesion. There were five patients who had both ALH and ADH; in only one of those was the atypical lobular hyperplasia present inside of the lesion.
What about subsequent cancer development in patients with benign mucocele-like lesions? There were no published papers on this until we published our experience in 2016. Here are the results: Out of 102 patients with mucocele-like lesion in the Mayo BBD cohort, 13 developed cancer. The mean age at which they developed cancer was about 66, and the mean interval between the biopsy of the mucocele-like lesion and cancer was approximately 15 years. The cancer was equally likely to be present in the ipsilateral breast versus the contralateral breast from the biopsy; and interestingly, out of the 27 patients with atypia, only 4 developed cancer. In summary, despite the high frequency of ADH and ALH, incidence of subsequent cancer is not significantly different than BBD cohort overall and atypia does not appear to connote highly elevated risk in this setting.
Here is an incidence curve of cancer development in the Benign Breast Disease Cohort and in the MLL patients. The red curve on the top shows the incidence curve for all atypical ductal hyperplasia. So we can see that if we follow these patients for about 10 years, their incidence of cancer as seen on the Y axis is a little over 10%. By the time they get out to 20 years, it is about 20%. Notice that the risk for patients with atypical hyperplasia continues and stays elevated throughout life, even after 20 years. The blue line, on the other hand, is the incidence curve for patients with proliferative disease without atypia. This would include patients who had adenosis, usual duct hyperplasia, papilloma, and so on. It shows significantly less cancer incidence than the patients with atypical ductal hyperplasia. So if you look at their cancer incidence at 10 years, it is about 5%, and it only gets to 10% at about 20 years or so. Now the other two lines are the patients with mucocele-like lesions. And notice that whether or not a mucocele-like lesion has atypia, their incidence curve for breast cancer overlaps almost completely with those patients who had proliferative disease without atypia. It was a surprise to us that patients with mucocele-like lesion, given the high-risk nature of them histologically, do not behave as though they have atypical ductal hyperplasia or atypical lobular hyperplasia, nor do they show an association with colloid carcinoma.
Here is the type of breast cancer that developed in our mucocele-like lesion patients. Most of them were generic ductal carcinomas. However, we had a couple of lobular carcinomas. None developed colloid carcinoma.
Now I said earlier that we need to discuss the need to excise a mucocele-like lesion when it is identified on a needle core biopsy, and here is a summary of four studies that looked at this particular issue. The top study found cancer in 4% of mucocele-like lesions (without atypia) who went on to excisional biopsy. In contrast, Park and Sutton did not demonstrate upgrades in any patients who did not have atypia. There were 4 out of 23 patients in the study by Ha et al. who were “upgraded”, but those were upgraded to atypia and not upgraded to cancer. So, of these four studies, there were a relatively small number of patients with mucocele-like lesions who were upgraded to cancer. All of those were present in patients with atypia; and even among those, the upgrade rate is relatively low. My take on this data and on the outcome data I showed you is that mucocele-like lesion, at least without atypia, is not an absolute indication for excision, although that decision should be guided by patient constitutional risk and the presence of post-biopsy residual imaging findings, such as residual microcalcifications or mass.
Here is a case of ductal carcinoma in situ, which is associated with a mucocele-like lesion, at least with extravasated mucin. I would not call this colloid carcinoma because, as you can see, the mucin is acellular. Recall that the mucin must contain floating epithelial cells in order to be characterized as colloid carcinoma.
The take-home points of this presentation are that mucocoele-like lesion is an uncommon but distinctive source of prominent mammographic microcalcification. When they are found by the mammographers, they almost always go to biopsy. It tends to develop in older age groups, and about a quarter of these patients have atypia, either ADH or ALH. The risk of upgrade after diagnosis on core needle biopsy is low, but not negligible. Interestingly, despite the high frequency of associated atypia, mucocoele-like lesions may not necessarily be associated with high risk. This is possibly because of the age association with mucocoele-like lesions. We know that patients of older age who have ADH or ALH are at lower risk than younger patients who have those same lesions. However, we are not certain why we did not see stronger risk association with mucocoele-like lesions. So we do not have evidence at this point that it should be considered an unstable or a high-risk precursor lesion.
Here is a reference from the Mayo Benign Breast Disease Cohort that summarizes our experience with mucocele-like lesion. It details some of the outcome in histologic studies I reviewed in this talk.

References

Mammographic Microcalcifications: A 58-year-old woman with worrisome mammographic microcalcifications.

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