Asian Journal of Surgery (2020) 43, 240–243

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.e-asianjournalsurgery.com

ORIGINAL ARTICLE

Co-existing malignant lesions in atypical ductal hyperplasia — Pathology, probability, predictors and prognosis

Michael Co [a], Tony Shek [b], Ava Kwong [a,*]

[a] Department of Surgery, The University of Hong Kong, Hong Kong
[b] Department of Pathology, Queen Mary Hospital, Hong Kong

Received 15 January 2019; accepted 30 April 2019
Available online 23 May 2019

KEYWORDS
Breast neoplasms;
Carcinoma;
Intraductal;
Noninfiltrating;
Risk factors;
Survival;
Pathology

Summary *Background:* Atypical ductal hyperplasia (ADH) is known to be associated with underlying malignant breast conditions. Previous studies have shown that up to 40% of ADH found in core needle biopsy of the breasts had undiagnosed malignant lesions after excision.
Methods: This is a retrospective study on a prospectively maintained database. From 1st January 2005 to 31st December 2014, a total of 262 excision or mastectomy specimens were identified to contain ADH. Clinical, radiological and pathological data were retrieved and analyzed. Correlating factors for the presence of co-existing pre-malignant or malignant conditions were analyzed. Overall survival in patients with or without co-existing malignant breast lesions were evaluated.
Results: 95 (36.3%) had co-existing malignant breast lesions within the same specimen. The median age at diagnosis was 49 (Range 17–85). Suspicious breast imaging features (BIRADS 4 or above) and lesions larger than 10 mm on breast imaging were independent risk factor for co-existing malignant pathology ($p < 0.001$ *and* 0.005 respectively).
After median follow-up interval of 60 months (6–120 months), the overall survival was comparable between the groups of patients having ADH with or without co-existing malignant pathologies (98.2% and 97.9% respectively).
Conclusion: Co-existing malignant lesions were present in up to 36.3% of the pathology specimens containing ADH, in which its presence could be predicted by pre-operative breast imaging.

* Corresponding author. Division of Breast Surgery, The University of Hong Kong, K1401, Department of Surgery, Queen Mary Hospital, Hong Kong.
E-mail address: avakwong@hku.hk (A. Kwong).

https://doi.org/10.1016/j.asjsur.2019.04.015

1. Introduction

Atypical ductal hyperplasia (ADH) of the breasts has been described to be associated with increased risk of invasive breast carcinoma.[1–4] ADH is usually considered as a borderline lesion within the spectrum of usual ductal hyperplasia and ductal carcinoma in situ (DCIS). ADH is known to be associated with increased risk of in-situ or invasive breast cancer, in which the risk of developing breast cancer can be as high as four to five times that of the general population.[1–5] This figure is even higher for premenopausal women, approaching a six-fold risk.[5] In patients with first-degree relative suffering from breast cancer, this risk is further increased to almost ten-fold.[1,6,7]

Distinction between DCIS and ADH can be ambiguous. Most pathologists adopt criteria derived from many series.[8–10] ADH was described initially as a diagnosis by exclusion. The recognition of some but not all of the features of DCIS (as well as the lack of the characteristics of usual-type epithelial hyperplasia) will be regarded as ADH.[1] Over the last few decades, the definition of ADH has been revisited and updated – while the diagnosis still rests on an absence of all the features of DCIS, additional supporting morphological features have been described.[11,12] Some proposed that diagnosis of ADH can be derived when morphological characteristics of DCIS are present but occupy less than two separate ductal spaces. Others use a 2-mm as the cutoff – lesions smaller than 2 mm in maximum diameter will be classified as ADH and larger ones as DCIS.[13] These criteria recognize essentially the same pathology. In general, ADH is usually small and focal, measuring no more than a few millimeters. Larger focus are accepted if associated with a radial scar/complex sclerosing lesion or a papilloma.

ADH is known to be associated with the presence of in-situ of invasive breast cancer. However, most studies in the literature focus mainly on evaluating the underestimation rate of ADH by core needle biopsy,[14–25] including a recent large series published on International Journal of Surgery in 2018.[25] In fact, very little evidence on the incidence of co-existing malignancy is known. Here we evaluate all our pathology specimens containing ADH after excisional surgery and we evaluate the incidence of co-existing malignant or pre-malignant conditions.

2. Material and methods

This is a retrospective study analyzing data from a prospectively maintained database maintained jointly by breast surgeons and pathologists in Queen Mary Hospital, a tertiary breast centre in Hong Kong. Data collection, access and analysis have been approved by Institutional Review Board of the Hospital Authority in Hong Kong. Patients with ADH found in excisional biopsy (including wide local excision) or mastectomy specimens were identified and retrieved. The study was registered with research protocol available at www.researchregistry.com. All surgical excisions were performed by the same group of board-certified specialist breast surgeon. Pathology specimens were reviewed by specialist breast pathologist. Patients with incidental co-existing malignant lesions were treated by standardized multidisciplinary management protocol for malignant breast conditions, drafted according to the National Comprehensive Cancer Network (NCCN) guidelines. Patient demographic, clinical, radiological and pathologic data were analyzed. Univariate and multivariate analysis were used to assess the correlating factors for the presence of co-existing malignant lesions in the specimens.

3. Results

From 1st Jan 2005 to 31st Dec 2014, 262 pathology specimens were identified to contain ADH. Median age of the patients was 49 (Range 17–85). All patients were female. All excisions were performed by specialist breast surgeons. Lesions with co-existing malignant pathologies were treated subsequently according to divisional protocol.

Out of the 262 specimens, 103 (39.3%) did not have identifiable co-existing pathology (i.e. pure ADH), 64 (24.4%) had co-existing benign lesions, including 36 fibroadenoma or fibrocystic disease, 22 intraductal papilloma and 6 benign or borderline phyllodes tumor. On the contrary, 95 (36.3%) specimens contain co-existing malignant lesions including 60 DCIS, 29 invasive ductal carcinoma (IDC); 2 lobular carcinoma in situ (LCIS), 1 invasive lobular carcinoma, 2 malignant phyllodes tumors and 1 angiosarcoma. Results were summarized in Table 1. Mastectomy was performed in 27 (28.4%) patients with co-existing malignant pathology. All final excision margins were clear of ADH or malignant tumors.

Risk factors for presence of co-existing malignant pathology were analyzed with univariate analysis (Table 2). Initial factors included age, family history of breast cancer, symptom, breast imaging characteristics and size of lesion on breast imaging. Suspicious breast imaging (BIRADS 4 or above), and size >10 mm were associated with increased risk for presence of co-existing malignant breast pathology ($p < 0.0001$).

Multiple logistic regression was subsequently performed with forward selection and probability of entry and removal equal to 0.05 and 0.1 respectively for model selection. Suspicious breast imaging features (BIRADS 4 or above) and lesion size larger than 10 mm on breast imagings remained independent factors for co-existing malignant pathology ($p < 0.001$, *and* $= 0.005$ respectively). Odd ratios were 8.463 (95% CI 4.307–16.627) and 7.519 (95% CI 1.843–30.675) respectively (Table 3).

Table 1 Different co-existing conditions in the pathology specimens with ADH.

Co-existing pathology	Number (%)
Atypical ductal hyperplasia alone	103 (39.4%)
Fibroadenoma/Fibrocystic disease	36 (13.7%)
Intraductal papilloma	22 (8.4%)
Phyllodes tumor (3 benign, 3 borderline)	6 (2.3%)
Ductal carcinoma in-situ	60 (23.1%)
Invasive ductal carcinoma	29 (11.1%)
Lobular carcinoma in-situ	2 (0.8%)
Invasive lobular carcinoma	1 (0.4%)
Malignant phyllodes tumor	2 (0.4%)
Angiosarcoma	1 (0.4%)

Table 2 Univariate analysis of risk factors for presence of nearby co-existing breast lesion (Chi-square test or Fisher's exact test, two tail, where appropriate).

Risk factors	ADH without nearly coexisting malignant pathology $N = 167$	ADH with nearby coexisting malignant pathology $N = 95$
Age		
<50	96	60
≥50	71	35
		$p = 0.3684$
Family history of breast cancer		
No	160 (1 unknown history)	94
Yes	6	1
		$p = 0.4279$
Presenting symptom		
Asymptomatic (screen detected)	38	13
Symptomatic (mass, pain, nipple discharge)	129	82
		$p = 0.0746$
Breast imaging		
Benign (BIRADS 1–3)	96	11
Suspicious (BIRADS 4 or above)	71	84
		$p < 0.0001$
Size of lesion on imaging		
<1 cm	3	70
≥1 cm	164	25
		$p < 0.0001$

Abbreviations: BIRADS = Breast Imaging Reporting and Data System.

After median follow up interval of 60 months (Range 6–120 months), there were three mortalities in the group without co-existing pathology. Overall survival (OS) was 98.2%. All three mortalities were related to cardiac event, sepsis and contralateral breast cancer respectively. In the group with co-existing malignant breast lesion, there were two mortalities (chronic renal disease and pneumonia). Overall survival (OS) was 97.9%.

Table 3 A multiple logistic regression for risk factors for presence of co-existing breast lesion.

Factors	p-value	Odds ratio (OR)	95% CI for OR	
Suspicious breast imaging (BIRADS 4 or above)	<0.001	8.463	4.307	16.627
Size ≥ 1 cm on breast imaging	0.005	7.519	1.843	30.675

4. Discussion

When ADH is found in the core biopsy of a breast lesion, total excision of the lesion is indicated due to a relatively high proportion of co-existing malignant or pre-malignant conditions. In literature, most studies document a relatively high rate of underdiagnosis of ADH by core biopsy. Studies have found that underestimation rate after subsequent excisions for ADH diagnosed on core needle biopsy can be as high as 69%.[14–20] However, a few other studies documented a much lower rate of carcinoma, ranging from 11% to 36%.[21–24] Reasons for such wide variation are not clear. In Asia, the rate of carcinoma/in-situ carcinoma detected after excision was reported to be around 40%.[25]

The definition of ADH is deceptively simple - there are three core components to the diagnosis of ADH, including architectural pattern, cytology, and extent of the lesion. However, the situation is more complicated when it applies to individual biopsy specimens, especially when inter-observer variability in the diagnosis is unavoidable. Certainly, the highly variable underestimation rate of malignancy for ADH diagnosed by core needle biopsy mentioned above could be related to different thresholds used for the diagnosis.

The significance of ADH lies in the fact that malignant or pre-malignant conditions may be present at the same time and by then, the management will be totally different.[25]

According to the results of this study, while age, symptom and family history of breast cancer of the lesion cannot accurately predict the presence of co-existing malignant pathology, we found that suspicious mammographic feature with large lesion size on imaging as the only predicting factors for the presence of co-existing malignant breast lesions. Although it is arguable that mammographic interpretation is also subjected to inter-observer variation; nevertheless, based on the above observation, we believe special attention should be paid on patients with core-biopsy proven ADH with suspicious mammographic features. Having said that, for most of the time, ADH appears as the only pathology or co-exists with other benign conditions that further treatment is not required after complete excision.

Survival analysis showed that the OS between the groups with or without co-existing malignant pathology were comparable. In fact, all mortalities in the current cohort were non-breast tumor related. Survival of patients having ADH with co-existing malignant pathology is not inferior to those without co-existing malignant conditions. This result reflects the fact that survival outcome of ADH with co-existing malignant lesion will not be compromised if the co-existing malignant condition is treated accordingly.

We recognize the inherent limitation of this study of being a retrospective in nature which is subjected to biases. However, the analysis is based on a sizable cohort of 262 pathological specimens containing ADH, in which to the best of our knowledge, represent one of the largest series in the literature.

5. Conclusion

Co-existing malignant breast conditions were present in up to 36.3% of the excisional specimens containing ADH. Its presence can be predicted by pre-operative breast imaging. However, co-existing malignant breast lesion was not associated with inferior survival outcome.

Conflicts of interest

The authors report no conflict of interests.

Disclaimers

This study is not funded by external source.

References

1. Page DL, Dupont WD, Rogers LW, et al. Atypical hyperplastic lesions of the female breast. A long-term follow-up study. *Cancer*. 1985;55:2698—2708.
2. Dupont WD, Parl FF, Hartmann WH, et al. Breast cancer risk associated with proliferative breast disease and atypical hyperplasia. *Cancer*. 1993;71:1258—1265.
3. Ma L, Boyd NF. Atypical hyperplasia and breast cancer risk: a critique. *Cancer Causes Control*. 1992;3:517—525.
4. Page DL, Jensen RA. Evaluation and management of high risk and premalignant lesions of the breast. *World J Surg*. 1994;18:32—38.
5. London SJ, Connolly JL, Schnitt SJ, et al. A prospective study of benign breast disease and the risk of breast cancer. *J Am Med Assoc*. 1992;267:941—994.
6. Tavassoli FA, Norris HJ. A comparison of the results of long term follow-up for atypical intraductal hyperplasia and intraductal hyperplasia of the breast. *Cancer*. 1990;65:518—529.
7. Page DL, Dupont WD. Indicators of increased breast cancer risk in humans. *J Cell Biochem*. 1992;50(suppl G):175—182.
8. Page DL, Dupont WD. Anatomic indicators (histologic and cytologic) of increased breast cancer risk. *Breast Cancer Res Treat*. 1993;28:157—166.
9. Connolly JL, Schnitt SJ. Clinical and histologic aspects of proliferative and non-proliferative benign breast disease. *J Cell Biochem Suppl*. 1993;17G:45—48.
10. Marshall LM, Hunter DJ, Connolly JL, et al. Risk of breast cancer associated with atypical hyperplasia of lobular and ductal types. *Cancer Epidemiol Biomarkers Prev*. 1997;6:297—301.
11. Page DL, Rogers LW. Combined histologic and cytologic criteria for the diagnosis of mammary atypical hyperplasia. *Hum Pathol*. 1992;23:1095—1097.
12. National Coordinating Group for Breast Screening Pathology. *Pathology Reporting in Breast Cancer Screening*. 2nd ed. Sheffield: NHSBSP Publications; 1995.
13. Tavassoli FA. Intraduct hyperplasias, ordinary and atypical. In: *Pathology of the Breast*. Connecticut: Appleton and Lange; 1992:155—191.
14. Jackman RJ, Nowels KW, Rodriguez-Soto J, et al. Stereotactic, automated, large-core needle biopsy of nonpalpable breast lesions: false-negative and histologic underestimation rates after long-term follow-up. *Radiology*. 1999;210:799—805.
15. Burbank F. Stereotactic breast biopsy of atypical ductal hyperplasia and ductal carcinoma in situ lesions: improved accuracy with directional, vacuum-assisted biopsy. *Radiology*. 1997;202:843—847.
16. Tocino I, Garcia BM, Carter D. Surgical biopsy findings in patients with atypical hyperplasia diagnosed by stereotaxic core needle biopsy. *Ann Surg Oncol*. 1996;3:483—488.
17. Gadzala DE, Cederbom GJ, Bolton JS, et al. Appropriate management of atypical ductal hyperplasia diagnosed by stereotactic core needle breast biopsy. *Ann Surg Oncol*. 1997;4:283—286.
18. Jackman RJ, Nowels KW, Shepard MJ, et al. Stereotaxic large-core needle biopsy of 450 nonpalpable breast lesions with surgical correlation in lesions with cancer or atypical hyperplasia. *Radiology*. 1994;193:91—95.
19. Acheson MB, Patton RG, Howisey RL, et al. Histologic correlation of image-guided core biopsy with excisional biopsy of nonpalpable breast lesions. *Arch Surg*. 1997;132:815—818.
20. Liberman L, Cohen MA, Dershaw DD, et al. Atypical ductal hyperplasia diagnosed at stereotaxic core biopsy of breast lesions: an indication for surgical biopsy. *AJR Am J Roentgenol*. 1995;164:1111—1113.
21. Lin PH, Clyde JC, Bates DM, et al. Accuracy of stereotactic core-needle breast biopsy in atypical ductal hyperplasia. *Am J Surg*. 1998;175:380—382.
22. Brem RF, Behrndt VS, Sanow L, et al. Atypical ductal hyperplasia: histologic underestimation of carcinoma in tissue harvested from impalpable breast lesions using 11-gauge stereotactically guided directional vacuum-assisted biopsy. *AJR Am J Roentgenol*. 1999;172:1405—1407.
23. Moore MM, Hargett CW, Hanks JB, et al. Association of breast cancer with the finding of atypical ductal hyperplasia at core breast biopsy. *Ann Surg*. 1997;225:726—731.
24. Brown TA, Wall JW, Christensen ED, et al. Atypical hyperplasia in the era of stereotactic core needle biopsy. *J Surg Oncol*. 1998;67:168—173.
25. Co M, Kwong A, Shek T. Factors affecting the under-diagnosis of atypical ductal hyperplasia diagnosed by core needle biopsies — a 10-year retrospective study and review of the literature. *Int J Surg*. 2018;40:27—31.