

Non-diagnostic Smears in Aspiration Cytology of Palpable Breast Lumps

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Abstract

The cytologic diagnoses of a wide variety of breast diseases have been described in the literature and cytologic appearances of some of these are not characteristic. Technical problems during aspiration and smear preparation influence the final diagnosis, therefore, even at best hands a non-diagnostic category is to be expected.

The objectives of this study were to determine the frequency of non-diagnostic reports and to assess the source of indecisiveness.

This study is based on a retrospective analysis of breast aspirates signed out by the first author over a period of 18 months. The smears with non-diagnostic reports were correlated with the available histologic follow-up to identify the problem area. Forty-eight (9.1 %) out of the 527 samples were non-diagnostic and within the recorded range of 6.9% to 20%. Of those 48 in the non-diagnostic category, 30 (62.5%) had histological follow-up. There were 11 (36.7%) malignant lesions and 19 (63.3%) benign lesions. In 23 cases (77%) pure interpretative problems and in 3 cases (10%) pure technical problems were responsible for the non-diagnostic reports. In 4 cases (13%) both factors contributed to the non-diagnostic report. Thirteen of the 30 (43%) lesions were cytologically suspected to be malignant. Of these 13, 9 (69%) were found to be malignant while only 4 were benign; thus non-diagnostic but suspicious lesions are more likely to be malignant. The commonest cytologic features responsible for problems at interpretation were high cellularity (37%), cell discohesion (30%), large nuclei and nucleoli (30%) and the small size of the cells (40%). Inadequate or low cell yield (86%), inadequate clinical history (14%) and poor staining (14%) contributed to technical problems. The cytologic diagnosis of breast lesions such as fibromatosis, complex sclerosing lesions, papillary lesions, angiosarcoma and low nuclear grade in situ and invasive carcinomas can be difficult and the cytologic criteria for these diagnoses need further evaluation.

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Introduction

A wide variety of neoplastic and non-neoplastic lesions have been described in the breast. Breast tissue is also subjected to many physiologic changes such as menstruation, pregnancy, lactation and ageing which lead to a spectrum of morphologic changes. The cytopathologist should be aware of all these changes and the relevant clinical details before assessing a breast aspirate. Various other technical problems pertaining to the fine needle aspiration biopsy (FNAB) procedure and smear preparation add to the complexity of interpretation. Therefore there are instances where the classical benign or malignant pattern is not observed; and benign lesions may show cytological atypia or a malignant lesion may show equivocal or suspicious features. Of utmost importance to the cytopathologist is the recognition of unusual features of common lesions and usual features of uncommon lesions.

Objectives

The objectives of this study were to assess the frequency of non-diagnostic reports in a series of breast aspirates and to determine the source of problematic cytological features, with emphasis on the lesions in which the cytological criteria are not very well laid down.

Materials and Methods

This study was conducted at the Department of Pathology, Faculty of Medicine, University of Colombo, Sri Lanka and Asiri Hospitals, Colombo, Sri Lanka.

All reports of breast aspirates signed out by the first author between July 1995 and December 1996 (18 months) were retrieved. The aspirations were performed by the pathologists, pathology registrars and rarely by clinicians. The smears were stained with haematoxylin and eosin (H&E). Mammography was not done in any of the cases.

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The non-diagnostic reports were those which did not have a conclusive benign or a malignant diagnosis, warranting a diagnostic excision biopsy or further investigations. Reports signed out as inadequate before review were not considered as “non-diagnostic/inconclusive”. All non-diagnostic cases which had histological diagnosis were reviewed in detail by both authors to determine the source of indecisiveness.

The terminology used for reporting breast cytology was based on the guidelines adopted by the National Coordinating Committee for Breast Screening Pathology in the United Kingdom¹ which included the 5 categories: inadequate, benign, atypical, suspicious and malignant. Atypical aspirates were those showing a predominant benign pattern with some unusual feature/features such as nuclear pleomorphism, cell discohesion or other nuclear or cytoplasmic changes not described in the common benign pattern. The suspicious aspirates were those with features highly suggestive but not diagnostic of malignancy.

True technical and interpretative problems were separated after review. The aspirates which had been categorised as atypical or suspicious before but declared inadequate after review and those with low cellular yield, inadequate-clinical history and poor staining were included in the group of technical problems. Aspirates which had less than 5 clusters of cells were declared inadequate.¹ Those with a few more than 5 clusters, but each cluster containing only a few epithelial cells were considered as low cell yield. Adequate, well-stained aspirates with atypical and suspicious features on review were included as true interpretative problems.

Results

Of a total of 527 samples, 48 (9.1%) were non-diagnostics. Of the 48 non-diagnostics, 30 had histological follow up. There were 11 (36.7%) malignant lesions and 19 (63.3%) benign lesions.

Table I shows the cytologic and histologic correlation of each case.

Thirteen of the 30 (43%) non-diagnostics were suspicious. These included 9/11 (82%) malignant and 4/19 (21%) histologically benign lesions. Nine (69%) non-diagnostic, suspicious lesions diagnosed at FNAB were malignant on histologic examination.

The 2 histologically malignant lesions (cases 20 and 25) which showed atypical but not suspicious features were an invasive duct carcinoma with a very low yield of small cells and a tubulolobular carcinoma. The 4 benign lesions which showed suspicious features included 2 cases of fibrocystic change with degenerative epithelial changes (cases 9 and 10), fibromatosis (case 11) and a complex sclerosing lesion (case 12).

In 23 cases (77%) pure interpretative problems were

TABLE I: CYTOHISTOLOGIC CORRELATION

Case numbers	Cytologic category	Histological diagnosis
1-5	A	Fibroadenoma
6-8	A	Fibrocystic change
9,10	S	Fibrocystic change
11	S	Fibromatosis
12	S	Complex sclerosing lesion
13	A	Lactation
14	A	Fibrosis: non-specific
15	A	Duct ectasia
16	A	Radiation
17	A	Foreign body granulomata
18	A	Phyllodes tumour
19	A	Gynaecomastia
20	A	Invasive duct carcinoma
21-23	S	Invasive duct carcinoma (nuclear grade 1-2)
24	S	Invasive duct carcinoma with extensive necrosis (high nuclear grade)
25	A	Tubulolobular carcinoma
26,27	S	Lobular carcinoma
28	S	Intracystic papillary carcinoma
29	S	Angiosarcoma
30	S	Micropapillary <i>in situ</i> carcinoma

A: atypical; S: suspicious

responsible for non-diagnostic reports.

In 3 cases (10%), non-diagnostic reports were due to pure technical problems. The aspirates in these (cases 1,6 and 20) showed a very low, unsatisfactory cellular yield. Therefore, the source of indecisiveness was purely technical. These should have been reported as inadequate at the outset. Although a repeat aspiration may have helped to arrive at a diagnosis, an excision biopsy was done without repeat aspiration as decided by the clinician.

In 4 cases (13%) both interpretative and technical problems contributed to the non-diagnostic report. Lactating history was not available at the time of diagnosis in case 13. In others (cases 25, 26 and 29) the technical problem was low cellularity in addition to interpretative problems. Poor nuclear staining was an additional technical problem in case 26. In case 25 (tubulolobular carcinoma), a repeat aspiration also showed a low yield of small atypical cells. In cases 26 and 29 the pathologist chose not to repeat the aspiration. The lesion was very small and deep-seated in case 26 (lobular carcinoma) which made localisation difficult, while histologic examination was recommended for case 29 based on FNAB and clinical suspicion of an angiosarcoma.

Table II shows the source/sources of indecisiveness in individual cases.

The commonest cytologic features responsible for non-diagnostic aspirates were high cellularity (37%), cell discohesion (30%), large nuclei and nucleoli (30%) and small size of the cells (40%). The technical problems were low or inadequate cell yield (87%), inadequate clinical history (14%) and poor staining (14%). Three of the 6 lesions with low cell yield were lobular carcinomas.

Cytologic features of some lesions in which diagnostic criteria were not very clear-cut are further described below.

Fibromatosis (case 11)

The smears showed a low yield with small atypical cells showing high nuclear cytoplasmic ratio, mild nuclear irregularity, and lack of benign bi-modal pattern. A few spindle cells were also noted. The appearance was suspicious of a sclerotic malignancy or a lobular carcinoma. Histologic examination showed mammary fibromatosis.

Complex Sclerosing Lesion (CSL) (case 12)

The smears showed fairly small atypical epithelial cells with focal cell discohesion and tubular structures (Fig. 1) together with regular ductal epithelial cells and bare oval nuclei. Two of the 4 smears were very cellular. The differential diagnoses included fibrocystic change with atypical epitheliosis and a tubular carcinoma (TC). Histologic sections showed features of a CSL. Some features mimicked a tubular carcinoma even at histology (Fig. 2).

Infiltrating Duct Carcinoma (case 24)

Extensive comedo type eosinophilic necrosis of one duct carcinoma somewhat resembled caseation; the cells with elongated footprint-like nuclei resembling epithelioid cells were noted in the smears (Fig. 3). A high grade infiltrating duct carcinoma with extensive necrosis was diagnosed at histologic examination. On review of the

TABLE II: SOURCE/SOURCES OF INDECISIVENESS IN EACH CASE

Case numbers	Histological diagnosis	Problematic cytological features
1	Fibroadenoma	Scanty, a few atypical cells (inadequate)
2,3	Fibroadenoma	High cellularity, discohesion, large nuclei and nucleoli
4,5	Fibroadenoma	High cellularity, discohesion
6	Fibrocystic change	Scanty, a few atypical cells (inadequate)
7,8,9	Fibrocystic change	Large nuclei and nucleoli
10	Fibrocystic change	Discohesion
11	Fibromatosis	Low yield, small and spindly atypical cells
12	Complex sclerosing lesion	Focal discohesion, small atypical cells, tubules
13	Lactation	High cellularity, discohesion, large nuclei, nucleoli
14	Fibrosis: non-specific	Low yield, small atypical cells
15	Duct ectasia	Large nuclei, nucleoli, debris
16	Radiation	Large nuclei, nucleoli, necrosis
17	Foreign body granulomata	Large nuclei, nucleoli
18	Phyllodes tumour	Large nuclei, nucleoli, large atypical cells
19	Gynaecomastia	High cellularity, mild nuclear atypia
20	Invasive duct carcinoma	Scanty, atypical cells (inadequate)
21,22,23	Invasive duct carcinoma (nuclear grade 1-2)	High cellularity, small atypical cells without the classic malignant or the benign bi-modal pattern
24	High grade invasive duct carcinoma	Abundant necrosis, epithelioid cells
25, 26, 27	Lobular carcinoma	Low yield, small irregular nuclei
28	Intracystic papillary carcinoma	Papillary clusters of epithelial cells, a few single atypical cells
29	Angiosarcoma	Bloody smears with a few atypical spindle cells
30	Micropapillary DCIS	Mixture of atypical and benign features, low nuclear grade

DCIS: duct carcinoma *in situ*

smears the presence of cells resembling epithelioid cells and the absence of high grade malignant cells were confirmed. However the epithelioid cells could not be demonstrated at histology in spite of extensive sampling.

Tubulolobular Carcinoma (case 25)

The smears were scanty with a small amount of atypical epithelial cells. A diagnosis was not possible partly due to the low cell yield in spite of a repeat aspiration. The histologic appearances were compatible with a tubulolobular carcinoma.

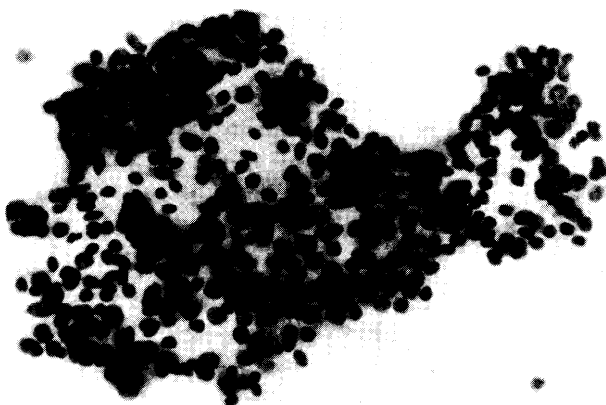


Fig. 1. Complex sclerosing lesion (H & E, x200). Fairly small epithelial cells with tubular differentiation.

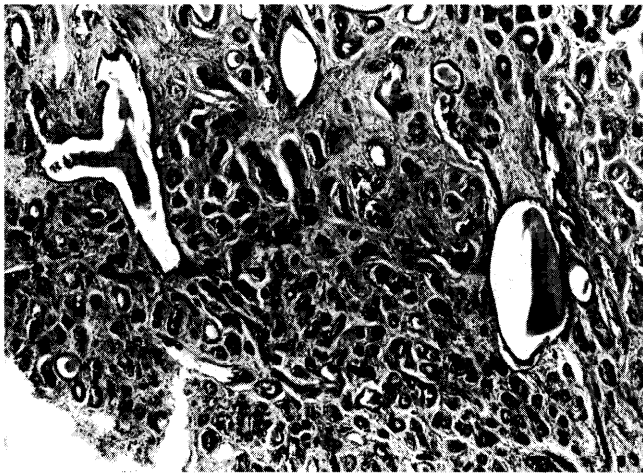


Fig. 2. Complex sclerosing lesion (H & E, x200).
Haphazardly arranged, attenuated, entrapped tubules within the fibrous stroma.



Fig. 3. An epithelioid granuloma in a high grade duct carcinoma (H & E, x400).
Footprint like nuclei of epithelioid cells in smears (arrow).

Intracystic Papillary Carcinoma (case 28)

The aspirates were from a breast lump in a 52-year-old lady. The smears were moderately cellular containing atypical epithelial cells forming well-formed papillary clusters with a few single intact atypical cells, cyst macrophages and abundant blood in the background (Fig. 4). The cells showed mild to moderate atypia (Fig. 5) and a few had a columnar configuration with very bland nuclei. No bare oval nuclei, apocrine cells or necrosis were noted. A papillary lesion, suspicious of malignancy was diagnosed and histologic examination was recommended. A fatty mass with a blood-filled cystic cavity was removed at surgery. The inner lining of the cyst was irregular. The wall showed small fleshy whitish areas. Histologic examination showed an intracystic papillary carcinoma with numerous poorly preserved papillary structures lining the haemorrhagic cyst. The wall of the cyst was infiltrated in a few areas.

Angiosarcoma (case 29)

The aspirate itself was heavily blood-stained and showed a few atypical spindle cells in a background of



Fig. 4. Intracystic papillary carcinoma (H & E, x40).
Papillary clusters in blood stained background.

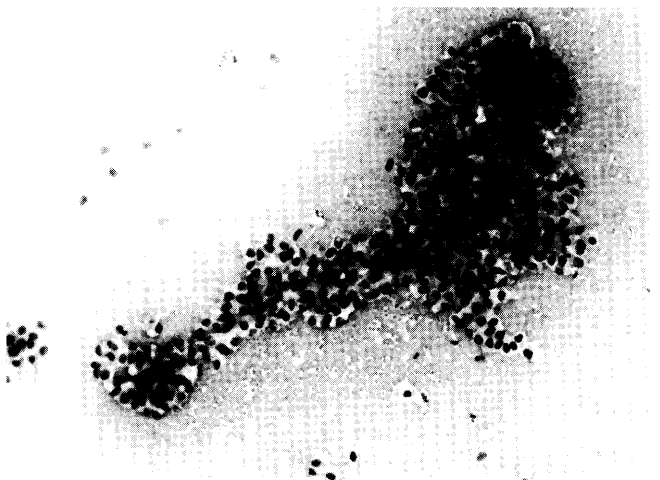


Fig. 5. Intracystic papillary carcinoma (H & E, x200).
Mild to moderate nuclear atypia with a few single cells.



Fig. 6. Intra duct carcinoma (Non comedo) (H & E, x400).
Low nuclear grade of in situ micropapillary carcinoma.

abundant blood. The cells were arranged in three-dimensional morules. This patient had a breast lump histologically diagnosed as haemangioma 8 months ear-

lier. An angiosarcoma was suspected and a grade 2 angiosarcoma was confirmed at histology. Atypia, spindle cells, heavy blood staining and the past history influenced the diagnosis. The low cellularity prevented a firm diagnosis.

Insitu Micropapillary Carcinoma-Low Nuclear Grade (case 30)

The patient was a 37-year-old lady. The smears showed cells with moderately atypical nuclei arranged in small and large sheets, a few papillaroid clusters and some single cells with intact cytoplasm together with large sheets of regular ductal epithelial cells in an abundant serous background. No necrosis or microcalcifications were seen. The appearance was suspicious of a carcinoma although atypical hyperplasia could not be ruled out completely. Histological examination showed extensive *in situ* micropapillary duct carcinoma with involvement of dilated ductular structures which were filled with fluid; the fluid component was noted in the aspirate as well. A few foci of *in situ* cribriform carcinoma were also present. The nuclear grade was low (Fig. 6). The low nuclear grade and mixing of neoplastic and non-neoplastic cells were the sources of indecisiveness.

Discussion

All published reports on experience of breast aspiration cytology carry a non-diagnostic category.^{2,7} The proportion of non-diagnostic smears (9.1%) recorded in our study is within the documented range of 6.9% to 20%.⁶ Lesions reported as non-diagnostic but suspicious are more likely to be malignant than those reported as atypical as shown in this series. The terms atypical or suspicious should be used in the correct context by the cytopathologists and correctly interpreted by the clinicians.

Fibromatosis

Cytological features of fibromatosis of the breast have been described in only a few publications and our findings support these reported findings.⁸ This is not a common lesion of the breast.⁹ The low cellularity and spindly fibroblasts are probable clues to this diagnosis although this is a rare lesion of the breast. Histologic examination is confirmative as cytologic appearances are not classic.⁹

Complex Sclerosing Lesion (CSL)

Lesions which are less than 10 mm are called radial scars (RS) while larger lesions are called CSL.⁹ Literature review showed an infrequent report which highlights the cytologic features of CSL/RS¹⁰ and those observed in this study are similar.

Tubular carcinoma is a malignancy which may present

as cohesive cell clusters with minimal atypia and tubular differentiation and myoepithelial cells without displaying overtly malignant features.^{9,10} These were the basic features we observed in case 12. The distinction between CSL and TC is difficult even at histology as experienced in this case.

Infiltrating Duct Carcinoma

A common problem encountered in this series was the presence of small minimally atypical nuclei in highly cellular smears (cases 21 to 23). These were highly suspicious but the minimal nuclear atypia precluded a diagnosis of malignancy. All 3 cases at histology were duct carcinomas with nuclear grade 1-2. Cytologic diagnosis of duct carcinoma of low nuclear grade can be a problem due to the presence of minimally atypical cells in spite of a cellular smear.

The absence of epithelioid cells in the histologic sections and of malignant cells in the smear in case 24 can be explained only by a sampling error. Epithelioid granulomas are known to be found in association with a malignant tumour

Infiltrating Lobular Carcinoma

The problems encountered in the cytologic diagnosis of lobular carcinoma due to low cellularity have been described by others.^{11,12} The single case of tubulolobular carcinoma in this study showed only a few small atypical cells without diagnostic features.

Intracystic Papillary Carcinoma

Differentiation of malignant and benign papillary lesions is difficult.¹³ A diagnostic clue to malignancy such as high cellularity associated with numerous single cells described by others¹⁴ was not seen in our cases. The diagnostic difficulty of papillary lesions continues.

Angiosarcoma

This was suspected partly by observing atypical spindle cells which formed cell balls; probably vasoformative structures. The past history of a haemangioma also influenced the diagnosis. The cellularity was inadequate for a confirmative diagnosis. However, the atypia noted in the occasional cell clump was significant enough to suggest an angiosarcoma.¹⁵ The differentiation of a grade 1 angiosarcoma and a haemangioma of the breast will certainly be a challenge to the cytopathologist in the future. The debate as to whether benign vascular neoplasms occur in the breast is probably settled now.⁹

Micropapillary in situ Duct Carcinoma (non comedo)

This diagnosis is difficult compared with that of comedo duct carcinoma *in situ* (DCIS), due to low nuclear grade.^{16,17} The cytologic features of micropapillary *in situ* duct carcinoma (non comedo) have not been de-

scribed in any publication in detail. The loss of classical benign pattern with mild or moderately atypical cells in clusters and groups forming papillaroid structures occurring with single cells with intact cytoplasm should raise the possibility. The differential diagnosis should include other papillary lesions.^{14,15} However, the low incidence of pure DCIS in a palpable breast lump and the problems of cytologic distinction between DCIS and invasive carcinoma should and will always be remembered by the cytopathologist.

Fibroadenoma and Fibrocystic Change

The two commonest benign lesions of the breast, fibroadenoma and fibrocystic change, were equally responsible for non-diagnostic reports. High cellularity and nuclear enlargement are common diagnostic pitfalls in fibroadenomata. This has been noted in previous studies.¹⁸⁻²⁰ Cell discohesion was another disturbing feature observed in 4 fibroadenomas in this series. A hormonal basis has been suggested for these atypical features.¹⁹ Hormonal changes are common in teenagers and premenopausal women, and also in women on hormone replacement therapy. The latter history was not available for any of our patients. Two patients in our series were in the premenopausal age group.

In cases 2 and 3 the additional atypical nuclear changes (enlargement and nucleoli) were due to unexpected secretory activity noted in the fibroadenomata. Secretory changes can also be responsible for cell discohesion.

Degenerative changes of cyst macrophages and exfoliated apocrine cells together with cell discohesion were responsible for atypical features in fibrocystic disease. These features seen in smears of breast lumps especially in older women can be alarming to the cytopathologist.

Miscellaneous Category

The atypical features seen in lactation, duct ectasia, radiation, phyllodes tumour and foreign body granulomata were similar to those described by other workers.^{20,21} Inflammatory and reactive changes of the ductal epithelial cells continue to trouble the cytopathologists. Therefore the clinical features would greatly benefit the final decision.

Conclusions

The non-diagnostic category (9.1%) in this series is comparable to others; the numbers may be reduced by repeat aspiration and strict adherence to criteria of adequacy of smears. All lesions with non-diagnostic cytologic reports, especially those with suspicious features should be investigated further or histologically assessed.

The commonest problematic cytologic features encountered were due to high cellularity, cell discohesion,

large nuclei with nucleoli and the small size of the cells.

Low cellularity was the commonest technical problem.

The cytologic criteria in the diagnosis of lesions such as fibromatosis, complex sclerosing lesions, intracystic papillary carcinoma, tubulolobular carcinoma and low nuclear grade *in situ* and invasive carcinomas need to be studied further. If there is a suspicion of any of these, an excision biopsy should be performed.

A good clinical history complements the cytologic diagnosis. It is well known that clinical features, mammography and FNAB together can give 99% to 100% accuracy in the diagnosis of breast lesions.

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REFERENCES

- Guidelines for cytology procedures and reporting in breast cancer screening, Cytology sub-group of the National Co-ordinating Committee for Breast Screening Pathology. Sheffield: NHSBSP Publication No 22, 1993.
- Kumarasinghe M P, Sherrffdeen A H. Aspiration cytology of breast lumps. *Ceylon Med J* 1993; 38:117-9.
- Sheige N. Fine needle aspiration of the breast; a review of 1,995 cases with emphasis on diagnostic pitfalls. *Diagn Cytopathol* 1993; 9:106-12.
- Stanely M W, Henry S M J, Zera R. Atypia in breast fine needle aspiration smears correlates poorly with the presence of a prognostically significant proliferative lesions of ductal epithelium. *Hum Pathol* 1993; 24:630-5.
- Mulford D K, Dawson A E. Atypia in fine needle aspiration cytology of non palpable and palpable mammographically detected breast lesions. *Acta Cytol* 1994; 38:9-17.
- Al-Kaisi N. The spectrum of "Grey Zone" in breast cytology a review of 186 cases of atypical and suspicious cytology. *Acta Cytol* 1994; 38:898-908.
- Willis S L, Ramzy I. Analysis of false results in a series of 835 fine needle aspirates of breast lesions. *Acta Cytol* 1995; 39:858-64.
- Zaharopoulos I, Wong J Y. Fine needle aspiration cytology of fibromatosis. *Diagn Cytopathol* 1992; 8:73-8.
- Rosen P I, Obermann H A. Tumours of the mammary gland. In: Rosai J, Sobin L H, editors. *Atlas of Tumour Pathology*. Third series, Fascicle 7. Bethesda: Armed Forces Institute of Pathology, 1993:58,59,297,298,306,307.
- Torre de la M, Lindholm K, Lindgren A. Fine needle aspiration cytology of tubular breast carcinoma and radial scar. *Acta Cytol* 1994; 38:884-90.
- Leach C, Howell L P. Cytodiagnosis of classic lobular carcinoma and its variants. *Acta Cytol* 1992; 36:199-202.
- Boppana S, Erroll M, Reiches E, Hoda S. Cytologic characteristics of tubulolobular carcinoma of the breast. *Acta Cytol* 1996; 40:465-70.
- Jeffery P B, Ljung B M. Benign and malignant papillary lesions of the breast. A cytomorphologic study. *Am J Clin Pathol* 1994; 101:500-7.
- Dawson A E, Mulford D. Benign versus malignant papillary neoplasms of the breast. Diagnostic clues in fine needle aspiration cytology. *Acta Cytol* 1994; 38:23-8.
- Carson K F, Hirschowitz S L, Nieberg R K, Sadeghi S. Pitfalls in cytologic diagnosis of angiosarcoma of the breast by fine needle aspiration: a case report. *Diagn Cytopathol* 1994; 11:297-300.

16. Venegas R, Rutgers J, Cameron B, Vargas H, Butler J. Fine needle aspiration cytology of breast ductal carcinoma *in situ*. *Acta Cytol* 1994;38:136-43.
 17. Malmud Y R, Ducatman B S, Wang H H. Comparative features of comedo and non comedo ductal carcinoma *in situ* of the breast on fine needle aspiration biopsy. *Diagn Cytopathol* 1992; 8:571-6.
 18. Bentoit J L, Kara R, McGregor S E, Duggan M A. Fibroadenoma of the breast: diagnostic pitfalls of fine needle aspiration. *Diagn Cytopathol* 1992; 8:643-7.
 19. Kordek R, Biernat W, Kubiak R. Breast fibroadenoma with atypical features-a case report. *Acta Cytol* 1996; 40:335-8.
 20. Greenberg M. Diagnostic pitfalls in the cytological interpretation of breast cancer. *Pathology* 1996;28:113-21.
 21. Dusenbery D, Frable W J. Fine needle aspiration cytology of phyllodes tumour. Potential diagnostic pitfalls. *Acta Cytol* 1992; 36:215-21.
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