

Cytology of mucinous carcinoma of breast: a report of 28 cases with histological correlation

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Abstract:

Pure mucinous carcinoma (MC) of the breast is a relatively uncommon variant of breast carcinoma with distinctive histological and cytological features. In this study we have analysed fine needle aspiration (FNA) cytological material from 28 cases of MC of breast and correlated the cytomorphological features with histopathology. The 28 patients consisted of 27 females and one male patient. 14 patients were Chinese, 10 were Indian and four were Malay. Their ages ranged from 38 to 90 with a mean at 52 years. The left breast was involved in 17 and the right in 11 cases. The duration of the lump varied from two weeks to 10 years. The cytological picture was characterized by abundant extracellular **mucin** giving a "sea of mucin" or "whirlpools of mucin" effect, in which were seen floating **clusters** of tumour cells with relatively bland cytological features. Myxo-vascular fragments were seen in 12 cases. Dissociated tumour cells showed a plasmacytoid appearance with eccentric nuclei. In four cases, the mucin was scanty in amount and the cellularity was high while in two cases, the **cellularity** was very low. Psammoma bodies were seen in cytological smears in one case. Histological study of excision or mastectomy specimens **confirmed** all 28 cases to be pure MC. Knowledge of the distinctive cytomorphological appearance of MC would enable correct identification of these lesions as malignant and prompt treatment that could further enhance the survival of these prognostically good breast cancers.

Key words: fine needle aspiration cytology, breast neoplasms, mucinous carcinoma

INTRODUCTION

Mucinous carcinoma (MC) of the breast is a distinctive, well differentiated type of adenocarcinoma, constituting 2%-5% of breast **cancers**.^{1,2} Pure MC of breast has been reported to have a more favourable **prognosis**³⁻⁵ than other well differentiated adenocarcinomas of breast, with a lower frequency of axillary node metastasis³ and excellent short term prognosis, especially when the tumour measures less than 5 cm in **diameter**.^{3,6} Fine needle aspiration (FNA) has been described to yield copious amounts of mucinous material in MC with a variable proportion of tumour cells.⁷ The tumour cells have been described as being generally small and fairly uniform with minimal **atypia**,^{1,7-11} and this may give a false impression of benignancy. The present report describes the spectrum of cytological features observed in 28 cases of MC of breast with histological correlation.

MATERIALS AND METHODS

The patients were first seen at the surgical clinic of Maulana **Azad** Medical College and associated Lok Nayak Jai Prakash Narain Hospital, New Delhi or at the Faculty of Medicine, University of Malaya, Kuala Lumpur, and referred to the cytopathologist (GJ) for FNA. FNA was performed using a 21 gauge needle attached to a 20 ml plastic syringe mounted on a handle for single-hand grip. The aspirates were deposited on to clean glass slides, smeared, air-dried, fixed in 100% methanol and stained with **May-Grünwald** Giemsa (MGG) stain. Wherever possible, smears were wet-fixed in 95% ethanol for Papanicolaou's stain or mucin stain. Histological material obtained from **lumpectomy** or mastectomy specimens was fixed in **formalin** and processed routinely. After evaluation of the Haematoxylin and Eosin stained sections and histological grading (Bloom & **Richardson's**),¹²

histochemical stains for mucin were done on selected sections in all cases. Immunostaining for oestrogen receptor (ER) protein was done in some of the cases using the standard avidin-biotin-peroxidase technique.

RESULTS

Twenty-seven patients were female and one male. 14 were Chinese, 10 were Indian and four were Malay. Their ages ranged from 38 years to 90 years with a mean at 52 years. The left breast was involved in 17 cases and the right in 11. All patients complained of a breast lump, the duration varying from two weeks to 10 years. Three of the patients had harbored the breast lump for eight, nine and a half and 10 years respectively. On examination, all patients had palpable lesions. Of these, nine were mobile masses that appeared clinically benign. Four had large tumours that occupied most of the breast. One patient presented with multiple local recurrences, lung and liver metastasis over an eight-year period.

Mammography was done in the nine cases that appeared clinically benign. In four cases the mammographic appearances were that of a circumscribed or lobulated mass or density with well-defined margins, interpreted radiologically as "benign". In the remaining five cases, slightly irregular borders or spiculated densities were present.

In all cases FNA provided a pre-operative diagnosis of breast carcinoma and a specific diagnosis of MC could be given in 25. In the remaining three cases, categorization as MC was possible on review of the cytological smears.

Pathological features

Gross features: The tumours varied in size from 1.5cm x 1.2 cm x 1 cm to the largest measuring 6.8 cm x 6 cm x 5 cm in size. They were well circumscribed or diffuse and formed by a current-jelly like mass held together by delicate septae except in two cases in which mucin was insignificant or not visible grossly. Foci of haemorrhage were also seen.

Microscopical features: Histological study of sections of the tumour showed that all the cases were pure MC. In 23 cases the bulk of the lesion was composed of mucin in which groups of tumour cells appeared to be floating (Fig.1). One of these showed only mucin pools with muciphages and very few areas of tumour. Three cases showed high cellularity with scanty extracellular mucin (grade-three tumours).^{3,12} These clusters were solid or exhibited acinar or

papillary formations with little desmoplastic reaction. Seventeen patients had grade-one tumours, while eight had grade-two tumours.^{3,12} Psammoma bodies were seen in one case (Fig. 2). 18/19 cases were ER-positive. The single negative case was a grade-three tumour. Two other grade-three tumours were ER positive.

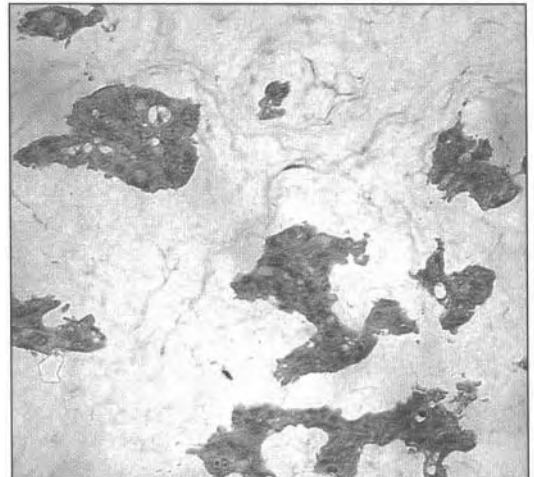


Fig. 1: Tumour cells floating in mucin in histological section of mucinous carcinoma. H&E x 150.

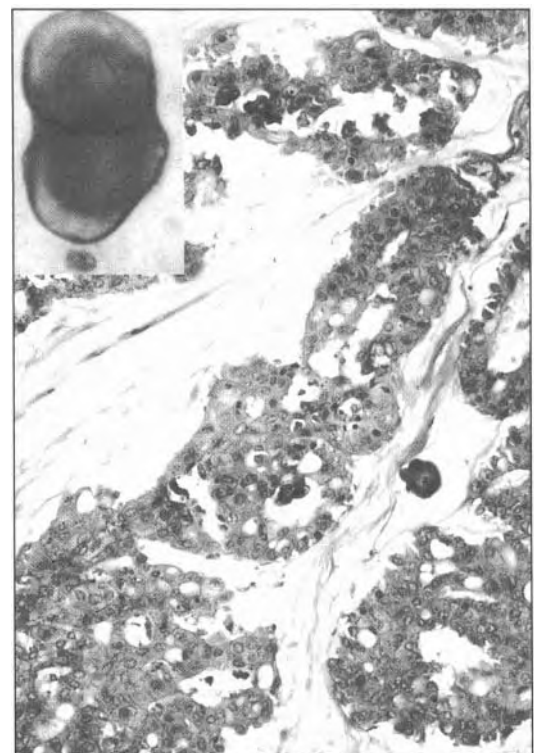


Fig. 2: Psammoma bodies in histological section of mucinous carcinoma. H&E x 300. (Inset) Psammoma bodies in cytological smear of mucinous carcinoma. Pap x 400.

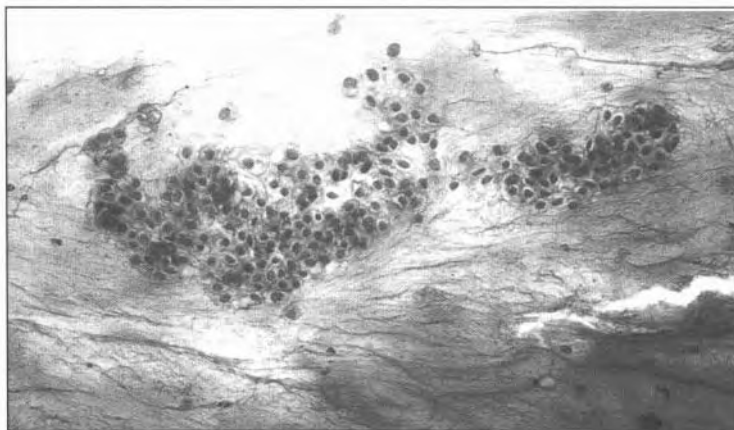


Fig. 3: Sheets of bland tumour cells surrounded by mucin giving a whirlpool effect. MGG x 200.

Cytological features: In 25 cases the cytological picture was dominated by the presence of ball-like, three-dimensional or loosely cohesive clusters of tumour cells, flat sheets and occasional single cells floating in a "sea of mucin" or surrounded by "whirlpools of mucin" (Figs.3 & 4). The mucin was present as homogenous or filmy, wispy extracellular material staining variably deep blue or bright pink (metachromatic) with MGG stain. In nine cases cellularity was mild with proportionately larger amounts of mucin. Two of these cases showed mainly histiocytes (muciphages) and only occasional clusters of tumour cells with a bland appearance (Fig. 5). In 16 cases, the ratio of cells to mucin was almost equal. In three cases the cellularity was high (Fig. 6), the characteristic "sea of mucin" feature was not seen with only small amounts of extracellular mucin present. Myxovascular fragments were seen in 12 cases

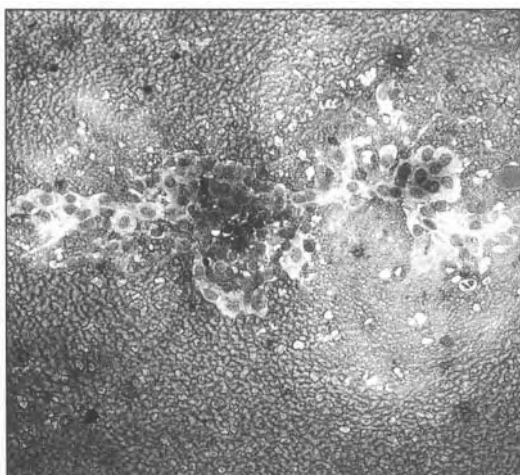


Fig. 4: Sheets of bland tumour cells in a sea of mucin. MGG x 250.

(Fig. 7) and psammoma bodies were seen (Fig.2 inset) in cytological smears in the case in which they were seen in histological sections. The cells were round to oval with eccentric or central, round or oval vesicular nuclei. Cells with eccentric nuclei (giving a plasmacytoid appearance) were prominent in three cases in which single cells predominated. Cells showed

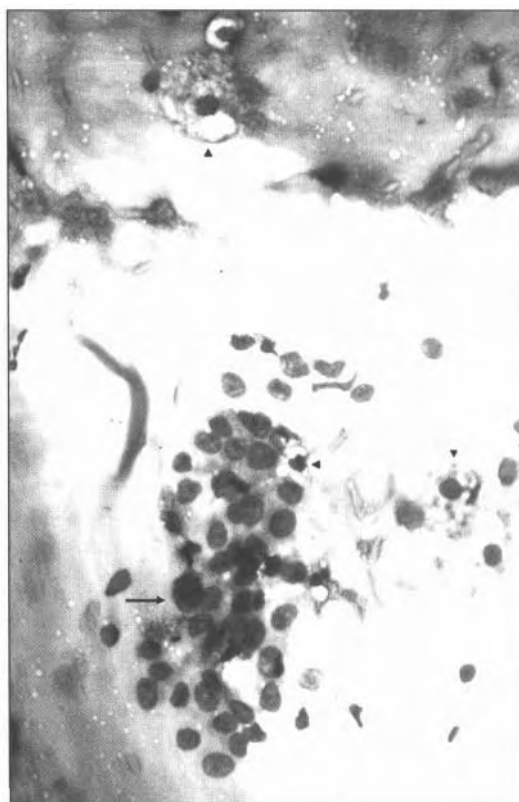


Fig. 5: Smear from mucinous carcinoma showing extracellular mucin, histiocytes (arrow-head) and occasional clusters of bland tumour cells (arrow).MGG x 300.



Fig. 6: Smear from mucinous carcinoma showing scanty mucin, high cellularity and branching vessels. MGG x 80.

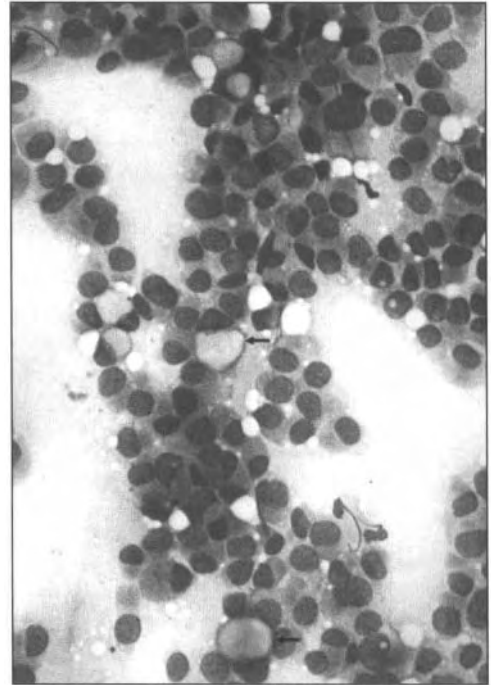


Fig. 8: Signet-ring cells (arrows) in smear from mucinous carcinoma. MGG x 400.

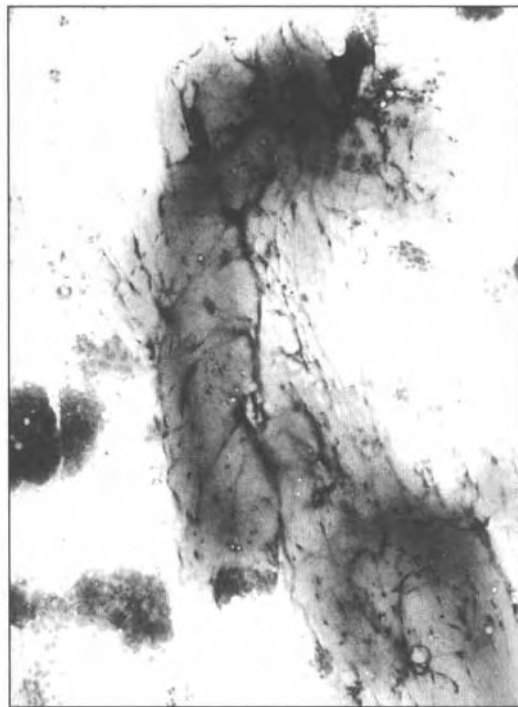


Fig.7: Myxovascular fragments in smear from mucinous carcinoma. MGG x 200.

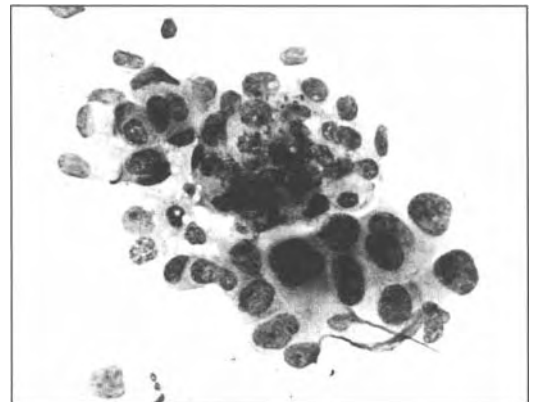


Fig. 9: Nuclear pleomorphism in cells of mucinous carcinoma. MGG x 400.

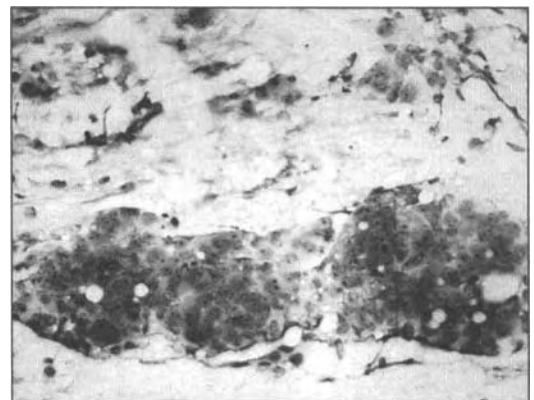


Fig.10: Macronucleoli in cells of mucinous carcinoma. MGG x 300.

a moderate amount of basophilic cytoplasm and cytoplasmic vacuoles were present in seven cases. Occasional signet ring forms were seen in four cases (Fig. 8). A few cells showed fine reddish (metachromatic) cytoplasmic granules. In 17 cases nuclear pleomorphism was minimal, but the nuclei were uniformly enlarged and had one or more micronucleoli. The remaining 11 cases showed mild or moderate pleomorphism with occasional macronucleoli (Figs. 9 and 10). Mitosis was seen in an occasional cell but was not a striking feature. A cytological diagnosis of MC was given in 25 cases and in the remaining three, a diagnosis of breast carcinoma was given, with the comment that the cytomorphology was compatible but not characteristic of MC.

DISCUSSION

FNA cytological reporting of malignant breast lesions does not usually include the categorization of tumour type. Some types of breast carcinoma, however, show only subtle cytological features of malignancy. Attempting to subcategorize the tumour type on cytological grounds is an exercise that enhances knowledge about the distinctive cytological features of special and uncommon variants of breast carcinoma. This practice also helps identify metastatic and rare non-epithelial malignancies that may occur in the breast.⁸ To the inexperienced eye, the relatively bland features of the tumour cells from MC may suggest a benign lesion. However, even while looking through the 4x or 10x objective, the "sea of mucin" or "whirlpool" effect of the extracellular mucin bathing these bland cells is a very distinctive clue to the identification of MC. This feature was seen in all cases in the present and earlier series.^{2,8-10} The mucin stained variably blue or metachromatic on MGG stain and appeared as homogenous filmy or wispy extracellular material. Fanning *et al*¹³ also described dense linear strands staining variably blue-green, violet, or pink with the Papanicolaou stain and bright pink with Romanovsky stains.

Intracellular mucin may be seen in tumour cells of MC but are more abundant in type B lesions that show predominantly clumps of cells (rather than a trabecular or festoon pattern seen in type A).¹⁴ Signet-ring cells, seen in four of our cases, have been stated as being rare or absent in pure MC of the breast but may be seen in mixed MC and invasive ductal carcinoma (IDC) of the usual type. Signet-ring cell carcinoma of the breast, defined as carcinoma in

which more than 20% of cell population is composed of signet-ring cells,¹⁵⁻¹⁶ may be of ductal or lobular origin. The signet-ring cell variant of ILC rarely has an extracellular component" and must be distinguished from pure MC and other carcinomas owing to their vastly differing prognoses.^{15,18}

The myxovascular fragments seen in more than half of our cases probably correspond to the "thin endothelial lined vessels lying in mucin" seen in 50% of Fanning *et al*'s cases of MC.¹⁷ The bland monomorphic features of pure colloid carcinoma¹⁹ may be the cause of false negative cytodiagnosis. In our opinion however, careful examination of these uniform cells in the 40x objective shows these cells to be larger than the cells of fibroadenoma (FA) and other benign lesions with larger nuclei and higher nuclear-cytoplasmic (NC) ratio. Besides, about 40% of cases showed focal mild or moderate nuclear pleomorphism with one or more macronucleoli. The presence of single cells (variable in number) in most cases of MC and the absence of bipolar naked nuclei (a common feature in FA) further help in the differential diagnosis. It appears that, although MC is characteristically a low grade malignancy with grade-one nuclear features,^{3,13} grade-two nuclear characteristics may be seen in a few cases. Dawson and Mulford²⁰ found that six of 45 cases showed grade three nuclear features. They however did not have the opportunity to review the histology in all the cases and it is possible that their nuclear grade-three tumours may have had an additional component of high grade IDC. Duane *et al*,² performing comparative morphometric evaluation of MC with other types of breast carcinoma and with benign proliferative lesions, found statistically significant increase in the mean nuclear axis product in MC as compared to FA, pregnancy adenoma and lobular carcinoma.

Secretory carcinoma of the breast, another prognostically favorable type of breast carcinoma, may (like MC), show uniform tumour cells and abundant metachromatic extracellular mucin. In this variant however, intracellular as well as extracellular mucin, many signet-ring cells, vacuolated cells, and in some cases mucoglobular structures resembling bunches of grapes²¹ may also be seen. Besides, the granular background metachromasia in smears of secretory carcinoma differs markedly from the "sea of mucin" appearance of MC.²²

Mucocele-like lesions of the breast, benign papillomas and FAs containing extracellular

mucin have been considered as differential diagnostic problems.^{13, 23-24} FAs with myxoid degeneration have been stated as being able to produce a similar "sea of mucin with islands of cells" effect as seen in MC.²⁴ In a cytology series of 651 benign breast lesions²⁵ that contained 223 FAs and in a subsequent series of 780 cases that included 178 FAs,⁹ we did not find any "sea of mucin" or "whirlpools of mucin" appearance in any of the FAs. Besides, in FA, the amount of mucin is usually limited and generally found in one sample or slide whereas it is abundant and consistently present in all of the smears of colloid carcinoma.⁷ Smears from FA generally show stromal fragments and bipolar nuclei that are not seen in MC.^{9, 24-25} and patients with FA are generally much younger than those with MC.^{7, 24}

Fanning *et al*¹³ described smears from mucocele-like lesions as showing abundant extracellular mucin and few cohesive flat sheets of epithelial cells with uniform round nuclei, indiscernible nucleoli and fine chromatin. Single cells were absent. They suggested that smears containing abundant extracellular mucin should be diagnosed as MC only when they were cellular and contained numerous single cells (in addition to clustered cells). Mesenora and Tabbara²³ reported an uncommon case of ductal carcinoma in which FNA smears showed features overlapping those of MC, mucocele-like lesion, lactating adenoma and intraductal papilloma. Evidence linking mucocele-like lesions to atypical ductal hyperplasia, intraductal carcinoma and invasive MC has been found.¹⁷ Therefore, cytological evaluation of breast lesions containing abundant extracellular mucin should be done carefully to diminish the likelihood of over-diagnosis and under-diagnosis. The observation by us and earlier investigators²⁰ that at least a proportion of MCs may appear clinically and mammographically benign underscores the importance of FNA cytology in the correct preoperative diagnosis of MC.

REFERENCES

- Suen KC. Atlas and text of aspiration biopsy cytology. Baltimore: Williams & Wilkins, 1990:109.
- Duane GB, Kanter MH, Branigan T, Chang C. A morphologic and morphometric study of cells from colloid carcinoma of the breast obtained by fine needle aspiration. Distinction from other breast lesions. *Acta Cytol* 1987; 31:742-50.
- Norris HJ, Taylor HB. Prognosis of mucinous (gelatinous) carcinoma of the breast. *Cancer* 1965; 18:879-85.
- Melamed MR, Robbins GF, Foote FW Jr. Prognostic significance of gelatinous mammary carcinoma. *Cancer* 1961; 14:699-704.
- Silverberg SG, Kay S, Chitale AR, Levitt SH. Colloid carcinoma of the breast. *Am J Clin Pathol* 1971; 55:355-63.
- Clayton F. Pure mucinous carcinoma of breast. Morphologic features and prognostic correlates. *Hum Pathol* 1986; 17:34-8.
- Gupta RK, McHutchison AGR, Simpson JS, Dowle CS. Value of fine needle aspiration cytology of the breast, with an emphasis on the cytodagnosis of colloid carcinoma. *Acta Cytol* 1991; 35:703-9.
- Jayaram G. Review article. Breast cytology. *J Cytol* 1995; 12:82-6.
- Jayaram G, Alhady SF, Yip CH. Cytologic analysis of breast lesions. A review of 780 cases. *Malays J Pathol* 1996; 18:81-7.
- Greenberg M. Diagnostic pitfalls in the cytological interpretation of breast cancer. *Pathology* 1996; 28:113-21.
- Zajicék J. Aspiration biopsy cytology: Pan 1. Cytology of supradiaphragmatic organs. In: Weid GL, editor. Monographs in clinical cytology. Seventh volume. Basel, S Karger 1974:179.
- Bloom HJG, Richardson WW. Histological grading and prognosis in breast cancer. A study of 1409 cases of which 359 have been followed for 15 years. *Br J Cancer* 1957; 11:359-77.
- Fanning TV, Sneige N, Staerkel G. Mucinous breast lesions: Fine needle aspiration findings. *Acta Cytol* 1990; 34:754-5.
- Capella C, Eusebi V, Mann B, Azzopardi JG. Endocrine differentiation in mucoic carcinoma of the breast. *Histopathology* 1980; 4:613-30.
- Kamiya M, Mizuguchi K, Yoshimoto M, Tanaka M, Motegi S, Matushima H, Ishizawa M, Nakamura K. Cytologic diagnosis of signet-ring cell carcinoma of the breast. 1998; 42:650-6.
- Hull MT, Seo IS, Batterby JS, Csicsko JF. Signet ring cell carcinoma of the breast. A clinicopathologic study of 24 cases. *Am J Clin Pathol* 1980; 73:31-5.
- Rosen PP. Mucinous carcinoma. In: Rosen's Breast Pathology. Philadelphia: Lippincott-Raven; 1997. p. 405-20.
- Rosai J. Breast. In: Ackerman's Surgical Pathology. 7th Ed. St. Louis: CV Mosby; 1989. p. 1216-24.
- Katayama Y, Kosaka K, Kumagai Y, Okusawa E, Kawashima H, Juumonji F, Miura K, Okamoto M. Quality control of fine needle aspiration cytology of breast lesions. *Rinsho Byori* 1995; 43:808-12.
- Dawson AE, Mulford DK. Fine needle aspiration of mucinous (colloid) breast carcinoma - nuclear grading and mammographic and cytologic findings. *Acta Cytol* 1998; 42:668-72.
- Shinagawa T, Tadokoro M, Takenchi E, Oikawa K, Kanasugi K, Kalabe Y. Aspiration biopsy cytology of secretory carcinoma of breast. A case report. *Acta Cytol* 1992; 36:189-93.
- Jayaram G, Looi LM, Yip CH. Fine needle aspiration cytology of secretory carcinoma of breast - a case report. *Malays J Pathol* 1997; 19:69-73.
- Mesonero CE, Tabbara S. Fine needle-aspiration

- cytology of ductal adenoma: report of a case associated with a mucocele-like lesion. *Diagn Cytopathol* 1995; 13 (3):252-6.
24. DeMay RM. The art and science of cytopathology. Chicago: ASCP Press; 1996. p. 877-8.
 25. Jayaram G, Gupta M. Fine needle aspiration of benign breast lumps: a review of experience with 651 cases. *Malays J Pathol* 1994; 16:29-38.