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ORIGINAL ARTICLE

Cytological and biochemical studies of breast cyst fluid

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Summary We determined the biochemical composition of fluid aspirated from 52 breast cysts and classified the cysts into types I and II on the basis of the potassium-to-sodium (K/Na) ratio in the fluid. In this study, we confirmed the presence of prostate-specific antigen (PSA) in some breast cyst fluids, regardless of whether cysts were type 1 or type 2, or benign or malignant. On immunohistochemical study, we found no direct correlation between the presence of PSA and progesterone receptors, which is at odds with the results of earlier reports. Current practice in cytologic study appears to favor the examination of bloody fluid. In this study, two samples found to contain malignant cells were cloudy or turbid. We therefore recommend that all cloudy or turbid cyst fluids should be subjected to cytologic examination. This study indicated that the potassium and sodium concentrations were not the same in multiple cysts in the same individuals. In addition, apocrine cells were observed in both type 1 and type 2 cysts. Therefore, breast cyst type cannot predict the natural history of cystic changes or indicate the likelihood of cancer. The finding of malignancy in two patients with type 2 cysts also supports this argument.

Introduction

Gross cystic breast disease (GCBD) is a benign disease of the human breast, which is commonly observed in premenopausal women. Several studies indicate that patients with GCBD have an increased risk of developing breast cancer.[1,2] Two major types of epithelium lining breast cysts can be defined histologically: (a) apocrine epithelium with acidophilic cells and (b) flattened epithelium with basophilic cells.[3]

Using needle aspiration, the biochemical composition of breast cyst fluid (BCF), including electrolyte content, was studied in an attempt to understand and define its possible role in the

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pathogenesis of GCBD.[2–5] Subsequently, it was observed that the potassium-to-sodium (K/Na) ratio can also be used to distinguish between these two types of cysts, type 1 cysts, with K/Na ratios >1.5, which have apocrine epithelium, and type 2 cysts, with K/Na <0.66, which are lined with flattened epithelium; an intermediate type has K/Na ratios of 0.66–1.5).[3,6] Other investigators, however, have used the ratio of Na to K instead to differentiate these two types.[2,3,7,8] The cysts with high K/Na ratios are primarily secretory, while those with low K/Na ratios can be transudative.[2,7] Women who have cysts lined with apocrine epithelium (type 1) might have a higher risk of the subsequent development of breast cancer than women who have cysts lined with flattened epithelium.[9,10] In addition to K/Na, prostate-specific antigen (PSA), a serine protease present in both free and bound forms and thought to be produced exclusively by the prostate epithelial cells, has also been identified in 43–65% of BCF samples examined.[7,11] Type 1 cysts tend to have higher total PSA than type 2 cysts, but it has not been possible to determine a significant association between total PSA and cyst type.[12]

It is generally believed that the metabolically active apocrine cells lining type 1 cysts are responsible for the production of PSA in BCF and that PSA in breast cancer is associated with the presence of steroid hormones and receptors; its presence seems to be a favorable prognostic indicator.[10,12–15] Breast epithelium surrounding the active apocrine-type cyst is able to produce, secrete, and accumulate a large amount of PSA by a mechanism that could initiate events leading to proliferative breast disease.[7] While studying a case of breast intracystic carcinoma with PSA in BCF, Mannello et al.[15] suggested that production and secretion of this serine protease might also originate in the neoplastic cells surrounding the cyst.

The molecular forms of PSA in BCF in which free PSA predominates are very different from those in the serum of male patients with prostate cancer, in which free PSA is only a minor component.[16,17] Borchert et al.[12] have observed that type 1 cysts have proportionally higher free PSA, and they propose that the free-to-total PSA ratio in BCF may be another biochemical marker of breast cyst types, in addition to the K/Na ratio. In this study, we examined BCF samples obtained by fine-needle aspiration (FNA) for free PSA, total PSA, and free PSA/total PSA ratio, in addition to the previously mentioned K, Na, and K/Na ratio. We then compared these results with those of the cytology examination.

Materials and methods

Patients

Between January 2001 and June 2002, 52 samples of BCF were taken for this study from women attending the breast clinic at Sun Yat-Sen Cancer Center: These patients had an age range of 26–61 years, with a mean of 45.8 years and a median of 46 years. In the majority of patients only one cyst was punctured; in nine patients, samples were taken from cysts in both breasts or from several cysts on the same occasion.

Specimens

BCF was obtained by FNA performed by a surgeon. The volume aspirated ranged from 2.5 to 50 ml.

Cytology

The fluid was immediately delivered to cytology laboratory for processing. The samples were centrifuged at 1000*g* for 15 min, and the supernatant was stored at $-20\,^{\circ}C$ until assayed for total and free PSA, Na, and K. Smears were prepared from the sediment. Riu[18] and Papanicolou staining was performed. The morphology of cells released into the cyst fluid was evaluated.

The personnel carrying out the cytopathology examinations were blinded to the results of the biochemical tests.

Immunohistochemical staining for PSA, estrogen receptors, and progesterone receptors was performed on the paraffin-embedded block, which was cut in sections 5 μm thick. Sections were mounted on poly L-lysine-coated slides, deparaffinized, rehydrated, and autoclaved for antigen retrieval. Staining was performed on an automated immunostainer (Tech Mate 500, Dako, Capenteria, Calif.) using the avidin–biotin method.[19] Antibody for PSA was obtained from the Dako Corporation, and antibodies for both estrogen and progesterone receptors were obtained from Novocastra Laboratories (Newcastle, UK). Antibodies were diluted 1:50 for PSA and estrogen receptors and 1:30 for progesterone receptors.

Biochemical methods

Total PSA was measured quantitatively by a microparticle enzyme immunoassay (MEIA) on AXSYM (AXSYM total PSA reagent pack, Abbott, Abbott Park, IL 60064) as per the manufacturer's instructions.