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ORIGINAL ARTICLE

Fine-needle Aspiration Cytology of the Breast

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ABSTRACT

Fine-needle aspiration cytology (FNAC) is an established, highly accurate, and cost-effective method for diagnosing lesions in different organs, including the breast. The method is minimally invasive without unwanted side effects. FNAC forms part of the triple assessment of breast lesions. Despite some shortcomings of the reporting categories, FNAC as part of the triple assessment has proved its value in describing the findings most accurately. The diagnostic impact depends on experience of the operator, quality of preparation, and diagnostic skills of the cytopathologist. The highest accuracy is achieved at centers with a multidisciplinary approach. FNAC is often palpation guided from palpable breast masses, whereas ultrasonography guidance is more widely used on nonpalpable lesions. Inadequate sampling with FNAC is particularly seen in collagenous lesions and in submitted specimens sampled by physicians lacking experience with the FNAC procedure. A diagnostic biopsy is recommended when FNAC provides scant material. FNAC is considered to be a safe method for screening purposes, although moderately less sensitive than core needle biopsy. FNAC is most accurate when experienced cytopathologists are available to assess the adequacy of the aspirated material and advise on additional aspirations for ancillary tests when needed.

Keywords breast cancer, cytology, FNAC, triple assessment

Fine-needle aspiration cytology (FNAC) is a simple, quick, and reliable as well as cheap technique for obtaining diagnostic material. True fine needles for breast aspirations were first introduced in the beginning of 1960s by Franzen and Zajicek at the Karolinska Hospital in Stockholm [1,2]. Being an oncologist, Franzen introduced standard May-Grunwald Giemsa stains on air-dried smears to allow for rapid interpretation (Figure 1A). Despite their success, it was not until 1980s that FNAC became widely used. The reasons included lack of confidence in the sensitivity and specificity of the procedure, fear of tumor implantation in the needle track, lawsuits, and surgeons not willing to relinquish the use of histological biopsy technique. The use of FNAC varies considerably in different centers. FNAC is commonly used as part of the triple diagnostic triad, which in addition to FNAC, includes clinical breast examination and radiology (mammography and ultrasonography). The diagnostic accuracy is close to 100% when all three modalities favor a benign or malignant diagnosis [3].

SPECIMEN ADEQUACY AND SAMPLING ERRORS BY FNAC

With respect to specimen adequacy, there are no current guidelines that are generally agreed upon in terms of required cell content. The definition of specimen adequacy in breast FNAC has been addressed by several authors [3,4]. Some centers adhere to the recommendations made by the Coordinating Committee for Breast Cancer Screening Pathology [3] and use five groups of epithelial cells as threshold of adequacy, while others leave the decision of adequacy to the discretion of the responsible cytopathologist. It is a general experience that in-house FNAC smears taken by experienced cytopathologists have substantially higher cell yield and are less frequently inadequate compared with smears submitted from other institutions [5]. The highest accuracy is achieved at centers with a multidisciplinary approach [6,7]. The main reason for false-negative specimens is sampling error and is mainly seen in small lesions <1 cm in diameter. Radiologists using modern high-resolution

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ultrasonography equipment detect more insignificant lesions that are difficult to sample. Finally, specimen inadequacy is frequently seen in lesions consisting of scar tissue and tumors with high content of connective tissue. Extensive fibrosis is frequently seen in radial scars and lobular carcinomas, and whenever FNAC specimen is inadequate or of poor quality a subsequent diagnostic biopsy should be taken [5].

CURRENT UTILIZATION OF BREAST FNAC

FNAC of the breast has two main goals. One is to confirm a radiological and clinical benign lesion and avoid unnecessary surgery and the other is to confirm a malignant diagnosis and allow definite treatment planning.

Centers using FNAC have adopted a multidisciplinary approach to the diagnosis of breast lesions, including participating experienced cytopathologists. Palpable and nonpalpable radiologic lesions are aspirated in cooperation with the attending radiologist. Air-dried direct smears are immediately stained with a rapid stain for microscopy (Figure 1A). The quality and amount of material is evaluated and in most cases a preliminary report may be given to the radiologist and the surgeon. Ultrasound (US) guided FNAC appears to be efficient in the management of patients with abnormal radiologic findings [8]. This approach allows the cytopathologist to visualize the ultrasonographic characteristics of the lesion and the needle placement to ensure cell sampling from the US identified lesion. When needed, additional FNACs for ancillary studies can be obtained. Cytological material and especially liquid-based suspensions are suitable for immunocytochemistry [9,10] (Figure 1B, C), and in situ hybridization [11] (Figure 1D). In case of diagnostic difficulties or discrepancy between radiological and cytological findings, a diagnostic biopsy may also be performed. Weekly conferences with key members of the multidisciplinary team, including cytopathologist, radiologist, breast surgeon, and oncologist, review cases to decide the best care for the patient [6, 7].

Both FNAC and core needle biopsy (CNB) are recognized as accurate diagnostic methods in separating benign from malignant breast lesions with high sensitivity and specificity [5,12–16]. Nonpalpable lesions are mostly examined by ultrasonography guidance [17–19]. FNAC is simple and cost-effective and allows for additional material to be acquired when needed.

Benign and inadequate FNAC diagnosis must be correlated with the clinical and/or US and mammographical findings, and in noncorrelative cases with equivocal or suspicious radiology, a diagnostic biopsy is warranted. An alternative use of breast cytology is on-site evaluation of core biopsy imprints for evaluation of representativity of ultrasonographical findings, such as microcalcifications.

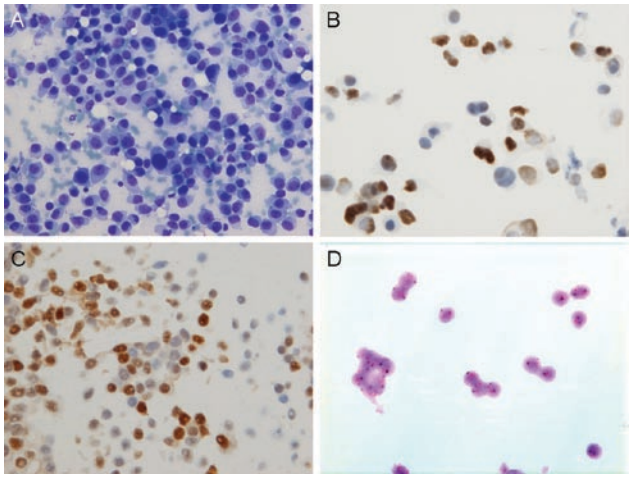

FIGURE 1 (A) Air-dried FNAC specimen with May Grunwald Giemsa-stained carcinoma cells (×200). (B) ER-positive carcinoma cells (×400). (C) PgR-positive carcinoma cells (×400). (D) DuoCISH specimen with carcinoma cells (×1000). Read signals in chromosome 17 and blue signals in HER-2 gene. Two signals from each marker. There is no evidence for HER-2 gene amplification.

COMMON INTERPRETATION ERRORS BY FNAC

The most common causes of false-positive FNAC diagnosis in breast pathology are fibroadenomas (Figure 2), complex sclerosing lesions, fat necrosis, and inflammatory conditions. Fibroadenoma usually display sheets of ductal epithelium and myoepithelial cells reflecting the histological features. Occasionally, fibroadenomas may display cytological atypia [20]. Myoepithelial hyperplasia may present with cellular pleomorphism and single cells simulating atypical cells. However, the nuclear chromatin is fine and evenly distributed. Poor smearing technique by an inexperienced aspirator may introduce artifacts simulating atypia. The recognition of bipolar

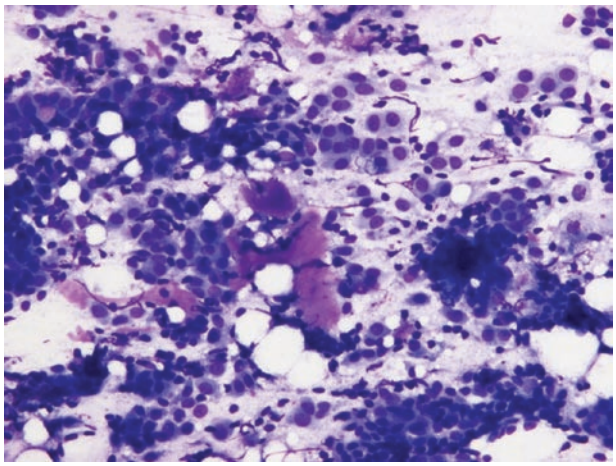

FIGURE 2 Fibroadenoma displaying proliferating epithelial cells surrounded by myoepitelial cells and a stromal fragment (×200).

myoepithelial cells and stromal fragments is particularly helpful in recognizing this as fibroadenoma.

Complex sclerosing lesions and radial scars are regularly seen in mammography screening cases. Complex sclerosing lesions are usually moderately to highly cellular with a pleomorphic pattern. These are radiologically suspicious and may be mistaken for low-grade carcinomas [21]. Fat necrosis, either post-traumatic or following surgery or radiotherapy or associated with mammary duct ectasi or fibrocystic disease, is reported to be another cause of both false-positive and false-negative FNAC diagnoses. Fat necrosis may be seen in most age groups and can persist for many years. The smears are characterized by macrophages that may be mistaken for atypical and malignant epithelial cells and variable number of multinucleated giant cells. The background usually displays fatty globules and fatty tissue, which is a useful aid in diagnosing fat necroses.

Radiotherapy usually causes severe changes in both stromal cells and epithelial cells, which display hyperchromatic cell nuclei that mimic malignant cells, but are usually few in number. Clinical history of performed radiative therapy is important. Finally, lactational changes in benign lesions may be misinterpreted as malignant cells. These milk-producing cells have large, active nuclei with prominent nucleoli and dense, granular chromatin. The vacuolated cytoplasm is fragile; therefore, only a few clusters of intact cells are usually found, but dispersed, naked nuclei are numerous. These dispersed, naked nuclei may give the visual impression of loose cohesion of cells, a feature associated with malignancy. High cellularity, dyscohesive cells, pleomorphism, hyperchromasia, prominent nucleoli, and even necrosis may strongly suggest cancer [22]. A history of pregnancy is extremely helpful in suggesting a benign diagnosis. Metastases to the breast are rare and the most frequent secondary tumor is malignant melanoma. The melanoma cells may mimic carcinoma cells and immunocytochemistry is helpful in identifying melanoma cells (Figure 3).

MORE DIAGNOSTIC CHALLENGES

Despite its indisputable merit, FNAC has some limitations. A major obstacle is the lack of experienced cytopathologists in many institutions. Proliferative (adenosis, fibroadenoma, complex sclerosing lesion) and borderline breast lesions, such as columnar cell lesion and intraductal and intralobular epithelial proliferation, may present findings that can be difficult to distinguish from low-grade carcinomas [14,21,23–30]. Complete sensitivity of FNAC diagnosis of grade 1 breast carcinomas is approximately 93% [25], which is only slightly lower than reported in all materials [26]. The main reason for giving a suspicious rather than a definite malignant diagnosis was sampling error (60%) [25]. Fibroadenomas are well-known causes of false-positive and false-negative diagnoses [31]. Papillary lesions may harbor a spectrum of tumors, ranging from plain benign papilloma, via cellular papillary lesions with and without cellular atypia, to papillary carcinomas (both in situ and invasive) [31–34]. In general, all papillary lesions should be excised and examined histologically.

The issue of trying to distinguish between in situ and invasive carcinoma in FNAC specimens [16,23,35–40], or, rather, the almost universal rejection of this, has led to rapid decline in the use of FNAC prior to surgery in cases that otherwise are suspicious for malignancy. Numerous reports in the cytological literature describe the features of high nuclear grade ductal carcinoma in situ (DCIS) (Figure 4) and these are based on a relatively large number of cases [23,36,39,41]. High nuclear grade DCIS fulfills all general criteria of malignancy. In a setting of radiological microcalcifications without tumor, the following is characteristic: highly atypical cells in large aggregates and dyscohesion, comedo-type necrosis, and amorphous calcifications [39]. Invasion criteria have been defined, but are used in only few breast centers [40,42]. Cases used for describing features of non-high nuclear grade DCIS are far less frequent [40]. In most instances the differential diagnoses of low-grade DCIS are benign, proliferative disorders.

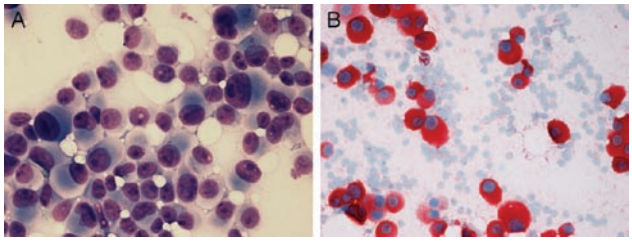

FIGURE 3 (A) Dispersed malignant cells in May Grunwald Giemsa-stained smear (×400). (B) Positive cytoplasmic melan A stain (×400).

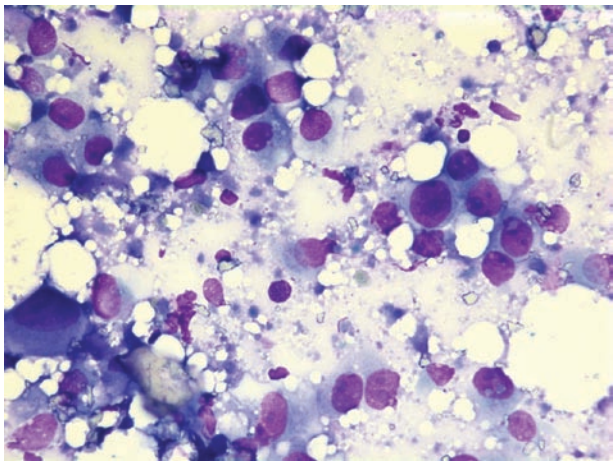

FIGURE 4 May Grunwald Giemsa-stained smear displaying carcinoma cells with severe nuclear atypia grade 3 and microcalcifications compatible with high-grade DCIS (×200).

FNAC VERSUS CNB

During the last decade there has been a shift from FNAC to CNB, partly because of a generally lack of experienced cytopathologists, but the above-mentioned limitations and controversies also contribute. Intervention radiologists and surgeons perform the majority of breast CNB on palpable and nonpalpable masses using ultrasound guidance.

The results of studies comparing FNAC and CNB for breast lesions are difficult to evaluate due to a number of variables. Firstly, both procedures have to be from the same lesion. The FNAC technique is dependent on the skill of the operator and the use of the triple test. For CNB, expertise in the technique and number and size of the cores taken will also influence accuracy. In guidelines for reporting breast FNAC, the National Breast Cancer Screening Programme suggests acceptable values for complete sensitivity >80%, specificity >60%, false-negative rate <5%, and false-positive rate <1% [3]. In a review by Pisano et al. the sensitivity and specificity of CNB was 91–99.6% and 98–100%, respectively [43]. In breast masses undergoing both FNAC and CNB, FNAC had an inadequate rate of 19.1% compared to 1% for CNB [5]. The figure for FNAC varies in the literature from <1 to 40% and is strongly aspirator dependent [44,45]. There is a well-recognized incidence of false-positive and false-negative diagnoses for FNAC due to inadequate sampling and interpretation errors. CNB procedure usually achieves adequate material and the core needle biopsies rarely are not representative reflecting the high specificity [46]. Still false-negative CNB may occur. Berner et al. compared FNAC with CNB diagnoses of palpable and nonpalpable breast lesions in a series of 4367 FNAC samples and 1248 corresponding biopsies. High specificity and sensitivity were achieved with both methods. False-positive and false-negative diagnoses were seen in 1.7 and 7.1% of biopsy-proven specimens sampled by FNAC when malignant and possibly malignant were grouped together. The corresponding values for CNB were 0 and 5.7%, respectively. Inadequate sampling with FNAC was particularly seen in collagenous lesions and in submitted specimens sampled by physicians lacking experience with the FNAC procedure [5]. Lieske and co-workers confirmed the advantage of combining FNAC and CNB. In their study including 2092 patients sensitivity of screening-detected breast cancers increased from 93% for CNB to 98% when both tests were used [46]. FNAC has the advantage of being more cost-effective than CNB and is the method of choice when examining multiple lesions, which is not possible by CNB. We consider FNAC to be a safe method for screening, although moderately less sensitive than CNB. CNB is used for preoperative diagnosis when FNAC provides scarce material and suspicion of a fibrotic or collagenous lesion, such as lobular carcinoma or a radial scar.

SUPPLEMENTARY DIAGNOSTIC PROCEDURES

FNAC samples are suitable for various molecular techniques that are currently available, i.e., flow cytometry, PCR, FISH, CISH, DNA image cytometry, gene analysis, including whole genome profiling, and cytogenetics [47]. Several reports have demonstrated the diagnostic and prognostic impact of applying FNAC material for further analyses [10,11,48]. But FNAC samples may vary in cell content. Thus, on-site evaluation is important to secure cellularity and representativity of the cell material.

FNAC AND TARGETED THERAPY

Targeted cancer therapy uses drugs that block cell growth and spread of cancer by interfering with molecular and cellular changes that are specific to cancer [47–49]. To date, predictive tests for solid tumors have focused primarily on the detection of defects in ER, PgR, AR, HER 2, EGFR, and KRAS. These molecular defects may include protein expression, gene amplification, or the identification of specific mutations within the genes themselves. In treatment of breast cancer hormone receptors like estrogen and progesterone receptors have for a long time been examined and used in routine treatment decisions. One major drawback is that quite often only primary tumor tissue has been analyzed. In metastatic breast cancer, it has been demonstrated that expression of estrogen/progesterone receptors and EGFR may be significantly different in metastatic lesions than in the primary tumor, which may impact therapeutic decisions [50]. Detection of Her 2 overexpression is important for targeted therapy with anti-Her 2 drugs [48]. With FNAC it is easy to obtain fresh material from metastatic lesions. Methods are established that enable all routine markers in breast cancer to be investigated on adequate FNAC material from metastatic lesions.

An extensive research focus has been on cellular tyrosin kinases and their role in cancer development. At present we are ignorant of interactions between various tyrosin kinase families, such as the EGFR family, the Eph/ephrin family, c-kit, and others. Several new inhibitors of EGFR and Her 2 are currently in development. The potential impact of EphB4 in oncology started in 1998. Now five preclinical and clinical trials are ongoing with drugs raised against Eph A2, Eph A 3, Ephrin A1, and Eph B4 [52]. Cardiotoxicity has been a major side effect of tyrosine kinase inhibitors [52]. Drugs like trastuzumab (Herceptin) against Her 2 receptor, imatinib against c-kit, bevacizumab (Avastin] against VEGFA, and others are all prone to this major side effect [52]. There is a growing recognition that these therapies are most effective when given to subpopulations of patients whose tumors contain the molecular defect targeted by the drug. FNAC-based material obtained from breast

cancer is ideal for making predictive tests that may help to achieve proper therapy decisions [48].

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