Indeterminate and Erroneous Fine-Needle Aspirates of Breast with Focus on the ‘True Gray Zone’: A Review

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Key Words

Breast cancer · Cytologic features · Fine-needle aspirate · Indeterminate · Erroneous

Abstract

Objective: To review our experience and the literature on inconclusive/erroneous fine-needle aspirates (FNAs) of breast with the focus on the ‘true gray zone’. To describe the cytology, differential diagnosis, pitfalls and limitations of common and rare lesions. **Study Design:** We conducted a literature search focusing on breast FNAs with statistical data of C3 and C4 categories including false-positive and false-negative cases. Similar data from 2003 to 2009 was obtained from our institution. **Results:** C3 and C4 categories account for 3–17% of breast FNAs. Contributing factors are technical difficulties, inexperienced pathologists interpreting FNAs of breast and overlap of cytologic features of certain benign and malignant conditions; this last, ‘true gray zone’ accounts for 2% of cases. Fibroadenoma, proliferative breast lesions, gynecomastia, infiltrating and in situ low-grade adenocarcinomas and tubular, cribriform, lobular and mucinous carcinomas are the most common problematic lesions. Granular cell tumor, adenomyoepithelioma, pregnancy-related lesions, fat necrosis, inflammatory and radiation changes, adenoid cystic carcinoma, spindle-cell lesions and

Phyllodes tumor are less common. **Conclusion:** Inconclusive/erroneous FNAs of breast due to the ‘true gray zone’ are rare. Most are due to the overlapping cytologic features of some benign and malignant conditions. Practical features that may help arrive at the correct diagnoses are elucidated.

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Introduction

Despite the apparent overall decline in its usage and its replacement by core needle biopsy (CNB), fine-needle aspiration (FNA) of breast continues to play a role in the initial evaluation of breast masses [1–3]. In many settings, FNA remains as accurate as CNB with less cost, complications and shorter turnaround times. The major shortcomings of FNA have been the inability to differentiate invasive from in situ cancer, the unease in interpretation of cytologic specimens among pathologists who are not trained in cytopathology or who do not routinely review these specimens and the presence of an indeterminate/‘gray zone’ category where a definite diagnosis of benign

The original data from the AUBMC was exempt from the local institutional review board; it was considered as QI/QA data.

or malignant is difficult. We reviewed our experience and the literature of the indeterminate/grey zone category including false-positive and false-negative (FP and FN) cases focusing on those FNAs with adequate and representative material (true gray zone). The cytologic features, differential diagnosis, pitfalls and limitations of the common and rare lesions are elucidated.

Definitions

Breast FNAs are placed into one of five diagnostic categories according to the uniform approach to breast FNA biopsy [4]:

- C1: Unsatisfactory
- C2: Benign
- C3: Atypical/indeterminate, favor benign
- C4: Suspicious, favor malignant
- C5: Malignant

Categories C1, C2 and C5 are usually straightforward and do not generally pose difficulties to pathologists.

An interpretation of atypical/indeterminate, favor benign (C3) is rendered when the FNA has characteristics of a benign aspirate (C2) but with features not commonly present in benign aspirates. These could be any, or a combination of nuclear polymorphism, some loss of cellular cohesiveness or nuclear and cytoplasmic changes resulting from hormonal or treatment influences. Increased cellularity may accompany the above features [4–6].

The category of suspicious, favor malignant (C4) is reserved for aspirates with some cells with features of malignancy where, however, the material is not diagnostic of malignancy because the specimen is scanty, poorly preserved or poorly prepared. Alternatively, the sample may show some malignant features of a greater degree than those observed in the C3 category without the presence of overtly malignant cells. Conversely, the sample may have an overall benign pattern with large numbers of naked nuclei and/or cohesive sheets of cells, but with occasional cells showing distinct malignant features [4–6].

An FN FNA is exemplified by an FNA that is classified as C2/benign and shows cancer upon follow-up and/or surgical excision. The incidence of FN breast FNAs ranges from 1–31% with an average of 10% [4–6]. The majority of these are due to sampling errors reflecting a quantitative problem in which there are few or no malignant cells on the smear. Quantitating the number of cells required for an adequate sample remains a source of controversy [4–7]. A minority of FNs, however, are due to a qualitative error. In these cases, the malignancies are gen-

erally in situ, low-grade or of a special type where malignant cells are present and clearly visible on the slide but are misinterpreted as benign [4–6].

An FNA that is classified as C5/malignant in which there is no malignancy upon follow-up and or surgical excision is categorized as FP. The incidence of FPs in FNA of breast is very low: 0–1% [4–6]. The most common causes for FP diagnosis are related to the inexperience of pathologists in FNA of breast and benign diseases that have a cytologic overlap with malignant lesions.

Factors Contributing to the Indeterminate/Erroneous Category

There are numerous factors that contribute to the indefinite, FN and FP categories. These include: (1) technical difficulties where the smears are limited by cellularity or obscured by drying artifact and or blood, (2) inexperience or unfamiliarity of the pathologist with the cytologic features of breast FNAs and (3) the overlap of cytologic features of certain benign and malignant conditions due to the nature of the lesion (true gray zone) [8–24]. The first 2 factors have accounted for the majority (up to 80%) of C3 and C4 cases whereas the ‘true gray zone’ represents a small fraction (20%) [9]. Interpretive categories C3 and C4 should not be abused and should not exceed 15% of all FNA diagnosis [4]. One major benefit of using the C3 and C4 equivocal categories is to reduce the frequency of misdiagnosis in the diagnostic C2 (FN) and C5 (FP) categories [4].

Adequacy

Strict criteria for the adequacy of a breast FNA would result in a decrease in the number of C3 and C4 cases. FNAs limited by cellularity and obscuring factors would be better classified as unsatisfactory. The criteria used for adequacy of solid nodules remains subjective. According to the uniform approach to breast FNA biopsy [4], an adequate specimen is one that leads to the resolution of a problem presented by a lesion in a particular patient’s breast. There is no specific requirement for a minimum number of ductal cells to be present [7].

Cytologic Features

The indeterminate categories have cytologic features that fall between clearly benign and clearly malignant aspirates. Benign FNAs are characterized by an adequate sample showing no evidence of malignancy. These samples are usually of low-to-moderate cellularity and consist

mainly of regular duct epithelial cells with characteristic benign cytologic features in a background of dispersed bare nuclei. Malignant aspirates, on the other hand, are characterized by moderately to highly cellular smears, often with a necrotic background, a monomorphic cell population, a conspicuous loss of cell cohesion, numerous isolated single cells with intact cytoplasm and a variable degree of anisonucleosis. Aspirates that fall into the C3 and C4 categories have some characteristics of both benign and malignant aspirates. Cytologic features deemed to be atypical include nuclear crowding, enlargement, overlap and some loss of cohesion [4–6]. Petersen et al. [8] identified certain cytomorphologic features that were helpful in distinguishing benign (atypical) from malignant (low-grade) lesions. Signs of malignancy were cell dissociation, arrangement in small clusters, nuclei greater than 16 μm , anisonucleosis, irregular nuclear borders, nucleoli and necrosis. Features in favor of benignancy were large monolayers, nuclei less than 16 μm without variation in size, smooth nuclear borders and bipolar nuclei in the monolayers.

Statistical Data

The incidence of C3 and C4 as reported in the literature ranges from 3–17% [5, 6, 9–16]. The highest incidence (14%) is found in stereotactic-guided FNAs [12]. Only a few studies clearly separate the causes of difficulty [9–15]. The true gray zone as reported by Al-Kaisi [9] is similar to our experience and represents around 2% of FNAs.

The proportion of samples classified as C3 and C4 varies in different centers. It increases with: (1) inexperience and poor technical skills of the aspirator, (2) inexperience and lack of FNA cytology (FNAC) training of the pathologist and (3) screen-detected/stereotactic-guided biopsies due to the higher incidence of ductal carcinoma in situ (DCIS), low-grade and special-type tumors sampled [11].

The number of cases classified as C3 and C4 are generally equal in most studies, with few studies reporting a predominance of C4 up to 71% [10].

Lesions Contributing to the Indeterminate/Erroneous Category

Fibroadenoma (FA), proliferative breast lesions [intraductal hyperplasia (IDH) with and without atypia, sclerosing adenosis (SA), radial scar/complex sclerosing

lesion (RS/CSL) and papillomas] and gynecomastia in males account for the most common benign lesions, with infiltrating low-grade adenocarcinomas of no special type, tubular, cribriform, lobular and mucinous and low-grade DCIS being the most common problematic malignant lesions. Less common lesions include granular cell tumor, adenomyoepithelioma, lactation- and pregnancy-related lesions, fat necrosis, inflammatory and radiation changes, adenoid cystic carcinoma (ACC), spindle-cell lesions and Phyllodes tumor (PT) [8–24].

Is There a Need for Two Separate Uncertain Categories (C3 and C4) or Should They Be Combined into One Equivocal/Suspicious Category?

Stratification of cases into C3 and C4 is beneficial, according to some experts, in that it identifies groups of patients who are more likely to have either benign (C3) or malignant (C4) outcomes. Large studies with histopathologic correlation have shown that in C3 category patients, there are benign outcomes in 47–87%, while in C4 category patients, there are malignant outcomes in 72–87%. A significant proportion of C3 patients, however, still have malignancies (13–53%), while a smaller percentage of C4 patients have benign disease (13–28%) [9–15]. Advocates of the 2 categories believe that patients with C3 lesions may not necessarily be subjected to surgical biopsies if their clinical examination and mammography findings are also benign (i.e. a negative triple test). A repeat FNA or CNB may be conducted (after at least 1 month allowing for reactive changes as a result of previous FNA to subside). If the second biopsy is benign (i.e. C2 and B2), then no surgical intervention or close follow-up are an option [10, 11].

Those that advocate a single equivocal/suspicious category believe that a CNB or surgical biopsy should be done for this combined category as the incidence of malignancy is significant in both subgroups [13, 15].

In a survey of preferences among surgeons who routinely use FNAC in their breast cases, there was no strong preference for either a 2 or 1 indeterminate/suspicious category [25].

The following is a discussion of the main categories of breast lesions with emphasis on FNA cytologic features and differential diagnoses.

Fig. 1. FNA of fat necrosis: macrophages, neutrophils and crenated red blood cells. Papanicolaou. $\times 40$.

Fig. 2. FNA of lactating adenoma: smears show foamy background material, cells with foamy cytoplasm and round nuclei with prominent nucleoli. Many nuclei stripped of their cytoplasm are noted. Papanicolaou. $\times 40$.

Clinical and Cytologic Mimickers of Malignancy

Fat Necrosis, Radiation Therapy, Lactation Changes, Granulomatous Mastitis and Granular Cell Tumor

Fat necrosis mimics malignancy, clinically, radiographically and histopathologically. FNA smears from fat necrosis show fat, amorphous debris, inflammatory cells, histiocytes and giant cells (fig. 1). The amorphous debris represents necrotic debris and degenerating fat which impart a foamy, granular and flocculent background. Calcified debris may also be present. The inflammatory cells are polymorphous nuclear leukocytes in the acute phase and lymphocyte and plasma cells in the organizing fat-necrosis phase. The histiocytes have abundant foamy lipid-filled cytoplasm. Multinucleated foreign body macrophages and numerous hemosiderin-laden macrophages may be present. Occasionally, fragments of fibrous tissue and newly found vessels (granulation tissue) may be observed. Epithelial cells are typically sparse but may show nuclear atypia. It is important to be conservative in the interpretation of malignancy when atypical nuclei are present in a degenerative and necrotic background with inflammatory cells and abundant macrophages, as reactive and reparative changes can result in atypia. It is equally important to recognize that the main cellular constituents are histiocytes and fibroblasts rather than epithelial cells [6].

FNA is used in new breast lesions in patients previously treated by radiation and lumpectomy/partial mastectomy to rule out recurrent malignancy. Radiation-induced changes in the breast include epithelial atypia, fat necrosis and poor cellularity. The epithelial atypia can be marked and mimic carcinoma. The most useful distinction from recurrent malignancy is rich cellularity and increased nuclear/cytoplasmic ratios. Loss of cell cohesion, anisonucleosis, conspicuous nucleoli and irregular nuclear membranes are helpful features, but can be seen to different degrees in benign radiation atypia [26–28]. Radiation-induced angiosarcoma is rare and presents as a skin or subcutaneous nodule several years after radiation. A high index of suspicion is a key factor in rendering an accurate diagnosis. Aspirates are usually bloody with spindle pleomorphic cells in a background of arborizing blood vessels. Comparison with the original breast carcinoma is most helpful in recognizing a second primary [6].

FNAC in pregnant and/or lactating women has a higher incidence of FP and FN diagnosis than in nonpregnant/lactating women [29–33]. FP results are due to the fact that the hormonal milieu of pregnancy and lactation leads to epithelial hyperplastic changes with cytologic atypia that can be readily misinterpreted as malignant. The incidence of FN diagnosis is also enhanced by the fact that the index of suspicion is low in this age group. Conversely, malignant tumors with round vesicular nuclei and central prominent nucleoli may be misinterpreted as

Fig. 3. FNA of granulomatous mastitis: a cluster of epithelioid histiocytes and few neutrophils. Papanicolaou. $\times 40$.

Fig. 4. FNA of granular cell tumor: large polygonal cells with abundant granular cytoplasm, small nuclei with fine chromatin. Papanicolaou. $\times 40$.

benign pregnancy changes and result in a FN diagnosis. Interpretation of breast FNAC in young women requires heightened awareness of the possibility of pregnant/lactating states; such information may not be routinely provided. The main features distinguishing benign breast conditions from malignancy in pregnancy and lactation are: cellular crowding, overlapped enlarged and pleomorphic nuclei with irregular nuclear membranes, coarse nuclear chromatin, mitoses and cellular dispersion in malignant lesions. Increased cellularity with nuclear atypia, single cells and a dirty background are seen in benign and malignant conditions [29]. Common lesions aspirated during pregnancy in decreasing frequency are lactating adenoma, FA with lactational change, galactocele and infiltrating duct carcinoma. The degree of lactational change varies with the gestational age [30]. Lactating adenomas are described as having moderate cellularity, abundant foamy background material, intact epithelial lobules or acini and small groups and solitary epithelial cells with uniform nuclei, fine chromatin and prominent nucleoli. When present, the cytoplasm is finely vacuolated. Many nuclei stripped of their cytoplasm are present [31, 33] (fig. 2). As highlighted by Gupta et al. [32], a team approach with close clinical correlation and follow-up made FNAC in pregnant women as useful as in nonpregnant women.

Granulomatous mastitis is a rare cause of C3 and C4 diagnosis [34–39]. It often presents as a mass that mimics carcinoma clinically and radiologically. It is usually

idiopathic, associated with lactation or, rarely, may be the result of tuberculosis, fungi, a ruptured epidermal inclusion cyst or a foreign-body reaction to suture or silicone implants. The inflammatory process may be associated with reactive epithelial atypia. Recognition of epithelioid histiocytes, multinucleated giant cells and scattered inflammatory cells help make the correct diagnosis (fig. 3). Correlation with clinical findings and culture are helpful.

Primary granular cell tumors of breast are uncommon and can clinically simulate malignancy. Aspirates are moderately cellular with isolated and clustered polygonal cells with abundant granular, foamy cytoplasm and small nuclei with fine chromatin [40–43] (fig. 4). Positive immunohistochemical stains for S100 protein and negative staining for cytokeratins and estrogen receptor/progesterone receptor support the diagnosis of granular cell tumor.

Biphasic Tumors

FA, Benign PT and Adenomyoepithelioma

FAs account for the largest single cause of false-atypical, false-suspicious and FP cases [8–16, 44–50]. They are most commonly confused with low-grade adenocarcinomas and rarely with PT [51–54]. FNAC of FA is among the most cellular of the benign breast lesions. In the typical aspirates, the smears are cellular and show three elements: stromal fragments, cohesive duct epithe-

Fig. 5. FNA of FA: tubular structure lacking abrupt change in diameter and pointed ends.

Fig. 6. FNA of benign PT: cellular stromal fragment traversed by blood vessels characteristic of PT but also seen in FAs. Papanicolaou. $\times 40$.

lial cells in large (staghorn) honeycombed, monolayered sheets and myoepithelial (ME) cells overlying the epithelial sheets and evident as single naked nuclei in the background. A mild degree of discohesiveness is commonly observed, i.e. single cells with intact cytoplasm; these should be disregarded when the clinical setting and physical and radiologic findings are typical. Due to the high cellularity, cellular discohesion, nuclear enlargement and prominent nucleoli seen in some aspirates of FA, these can be readily confused with low-grade adenocarcinomas. FAs may also show a few rigid tubular structures similar to those found in tubular carcinoma (TC), but they lack abrupt change in diameter and pointed ends (fig. 5). The epithelial cells of FA are slightly larger than those of normal benign duct cells but not as large as carcinomas. The polarity of the nuclei in the epithelial clusters is preserved in FA, whereas in carcinoma this is lost. The naked nuclei of FA are bland, small and oval; if they are present in carcinomas, they are naked tumor cell nuclei which are larger, more irregular and resemble the nuclei of the surrounding malignant cells. The vast majority of FAs with 'atypia' on FNA are conventional FAs [44]. Fewer cases are attributable to FAs with more complex proliferative lesions such as IDH, apocrine change and SA [44–46]. Conversely, there is also the potential for underdiagnosing breast carcinomas as FA. Intraductal, low-grade carcinomas of no special type and TCs may show stromal fragments and cohesive bland-appearing epithelium with small, naked, tumor-cell nu-

clei mimicking FA. Helpful differentiating features in some cases may be the clinical setting and the feel of the needle while performing the aspirate, rather than the cytology. In general, in young women, well-circumscribed, movable masses in the breast which feel rubbery upon aspiration are more likely to be FAs, whereas in older women, ill-defined, fixed masses with a gritty feel are more likely to be carcinomas. That said, there are cases where the distinction is impossible and an equivocal diagnosis is unavoidable.

Cellular stromal fragments have been used by some to distinguish FA from PT [51] (fig. 6). Many studies, however, have found this to not be reliable due to the variable thickness of the fragments produced by FNA sampling and smearing [52–54]. The presence of blood vessels in the stromal fragments is considered characteristic of PT but may be seen in FA. Significant stromal nuclear abnormality and increased or abnormal mitotic figures are features of malignant PT. On occasion, the epithelial proliferation in PT can be so extensive as to mimic carcinoma. PT should be suspected over FA when the mass is >4 cm and manifests rapid growth. Caution should be exercised in diagnosing carcinoma in the presence of a large, circumscribed mass with stromal hypercellularity.

Adenomyoepithelioma is a rare benign neoplasm of the breast with a biphasic proliferation of epithelial and ME cells. Smears are cellular with large clusters of epithelium and myoepithelium [55–66]. The ME cells can

Fig. 7. FNA of adenomyoepithelioma. **a** Bland epithelial cells surrounded by few ME cells showing enlarged nuclei with intranuclear inclusions (arrows). **Inset** Epithelioid ME cells with vacuolated cytoplasm mimicking macrophages. Papanicolaou. $\times 40$. **b** Spindled ME cells. Papanicolaou. $\times 40$.

be difficult to recognize. They are spindled, epithelioid, clear-cell or plasmacytoid. Their vacuolated cytoplasm is best appreciated on the Diff-Quick stain. Intranuclear cytoplasmic inclusions are described in one third of cases (fig. 7). Intranuclear inclusions are not specific to adenomyoepithelioma, but have been described in benign proliferative breast lesions [67], male breast carcinoma [68], myofibroblastoma [69] and myxofibrosarcoma [70]. Mild-to-moderate nuclear atypia is not uncommon and has led to FP diagnosis. To accurately identify the ME cells, immunohistochemical stains such as p63 or smooth muscle actin may be helpful.

Proliferative Breast Lesions

IDH with and without Atypia, SA or RS/CSL

Proliferative breast lesions represent the second most common cause of false-atypical, false-suspicious or FP cases in the literature [9–15]. The majority are non-palpable, mammographically detected lesions, although rarely, they may present as palpable masses. Their cytologic features overlap with those of low-grade carcinomas. The criteria used to diagnose proliferative lesions of duct epithelium in FNAC are similar to those used in histology and include architectural and cytologic features. Sneige and Staerkel [71] found that these features are well represented on aspiration smears. FNAC of IDH without atypia is characterized by epithelial cell groups

with complex cellular arrangements and irregular intercellular spaces with adjacent cellular streaming or nuclear spindling. The cells may vary in size and shape with a bland chromatin pattern. Single cells with intact cytoplasm are rare. Low-grade ductal carcinomas, on the other hand, are characterized by a monomorphic cell population of small-to-intermediate epithelial cells arranged singly or in clusters. Cell clusters are usually 3-dimensional with a papillary, solid or cribriform (regular round/oval spaces with surrounding, uniform, rounded cells) pattern. Individual cells are polygonal or cuboidal with round-to-oval nuclei and occasional small nucleoli [71–79]. ME cells within epithelial clusters and in the background are usually absent. Atypical duct hyperplasia is difficult to recognize on FNA smears and shows features common to IDH and low-grade ductal carcinoma [77–79]. This reflects the same difficulty encountered in histology. SA and RS/CSL are usually small, mammographically detected lesions; however, when confluent, they may present as a palpable, poorly delineated mass. The cytologic features of SA are characterized by variable cellularity, small-to-large groups of bland epithelial cells that focally form cohesive groups/tubules or occasionally discohesive clusters and individual cells. Acinar sheets are found in most cases. Cohesive, ball-like clusters of proliferating ductules admixed with dense connective tissue are usually seen. The stromal component consists of characteristically small, dense, hyalinized, fibrous fragments occasionally attached to the epithelial

Fig. 8. FNA of SA. **a** Tubular structures with bulbous ends and background ME cells. Papanicolaou. $\times 40$. **b** Corresponding surgical pathology. HE. $\times 40$.

sheets. Some tubules have an angulated configuration mimicking TC. ME cells are present in the background, but are not always associated with the small epithelial fragments (fig. 8) [80, 81]. Difficulty arises when aspirates show atypical features such as angulated tubules, discohesive individual cells, scant ME cells and nuclear atypia being noted concurrently [80]. Tubules with an angulated configuration or pointed ends, seen in SA, are usually a feature attributed to TC. TCs are more frequently hypercellular and the abnormal tubules are more abundant and diffuse and have a more rigid outline or acutely angled configuration. Discohesive cells are also more abundant [82–86]. Single cells with intact cytoplasm could mimic lobular carcinoma. In a large study of FNAC of RS/CSL [87], a C3 or C4 diagnosis was rendered in more than half the cases. RS/CSL were cytologically characterized by a mixed cell picture in which bipolar, naked nuclei, large and small cohesive epithelial sheets, apocrine cells, foam cells and elastoid stromal fragments were seen in various degrees. Papillary clusters, calcifications and tubular structures without rigid configuration associated with ME cells were also described. High cellularity, dirty background, tubular structures and dyshesion has led in some cases to the C3 and C4 diagnosis. The cytologic features are not specific and a diagnosis of RS/CSL can only be suggested when taking into consideration the radiologic appearance of the lesion [87–92].

Mammary Carcinoma and Its Variants

DCIS, TC, Invasive Ductal, Cribriform, Lobular and ACC

Ductal adenocarcinoma, no special type and of low nuclear grade accounts for the most common cause of FN, falsely atypical and falsely suspicious cytology diagnosis due to its common occurrence. Similar to the higher-grade counterparts, the smears are cellular with conspicuous loss of cell cohesion, scattered, individual tumor cells with intact cytoplasm and aggregates of 3-dimensional clusters, syncytial groups or occasional gland-like arrangements. Nuclear enlargement and atypia, by definition, are minimal [4–6].

High-nuclear-grade DCIS is readily diagnosed as malignant on FNAC. Low-nuclear-grade DCIS is problematic and is characterized by moderate-to-high cellularity, monomorphic, uniform, neoplastic cells with cribriform, solid or micropapillary patterns. The absence of ME cells helps distinguish it from benign proliferations. A distinction between invasive low-nuclear-grade carcinomas and in situ lesions is not possible [71–79].

The diagnosis of TC by FNAC is difficult with less than 50% of cases classified as C5 [82–86]. The characteristic findings include tubular structures, noteworthy dissociation, paucity of myoepithelium and cellular atypia [86]. The tubules in TC are usually numerous, rigid and with an abrupt change in diameter often ending in pointed tips (fig. 9a). They have abnormal angles with duct arms going

Fig. 9. FNA of TC. **a** Rigid tubules with abrupt change in diameter (long arrows) ending in pointed tips (arrow-heads). Few stripped ME cell nuclei in background (short arrows). Papanicolaou. $\times 40$. **b** ME cell nuclei seen on a plane above a cohesive group of epithelial cells (white arrows). Papanicolaou. $\times 40$.

off in unexpected directions at branching spots and are sometimes even without branching, resembling a bent elbow. Tubules may also have coma-shaped projections. Fibillary stromal aggregates, intracytoplasmic vacuoles resembling those of lobular carcinoma and the presence of nuclear grooves are helpful diagnostic criteria. ME cells may be numerous (fig. 9b). It is the presence of numerous ME cells, minimal dissociation and lack of significant cytologic atypia in some cases that results in an FN diagnosis of FA. Rigid tubular structures can be seen in FAs; however, FAs usually have a more prominent ME component, less discohesion and no/minimal cytologic atypia. Aside from the cytologic differences, the distinction becomes clearer when the pathologist performs the aspirate and can assess the difference between the gritty carcinoma and the rubbery FA.

The diagnosis of cribriform carcinoma is difficult on FNAC due to the relative cohesive nature of the malignant epithelium and the low nuclear grade [93–96]. Key to arriving at the correct diagnosis is recognizing cribriform as opposed to honeycombed architecture in the large sheets, absent-to-sparse ME cells and low nuclear grade. Osteoclast-like giant cells have been described more commonly in invasive cribriform carcinoma, although they have also rarely been reported in the in situ counterpart (fig. 10). Their presence should raise the suspicion for invasion [93–96].

Classic lobular carcinoma is associated with the highest FN rate among all types of mammary carcinoma. This

Fig. 10. FNA of invasive cribriform carcinoma: large sheets of cohesive epithelium with cribriform (cookie-cutter) architecture (arrows). Papanicolaou. $\times 20$. **Inset** Osteoclast-like giant cell more commonly seen in invasive carcinoma. Papanicolaou. $\times 40$.

is either due to sampling error related to paucity of tumor cells as a result of associated desmoplastic stroma or interpretive errors due to small cell size and subtle cytologic atypia of the tumor cells. FNAC slides are of variable cellularity. The cells are small and uniform with small nuclei. They present as single cells, Indian files or small balls.

Fig. 11. FNA of invasive lobular carcinoma: small tumor cells with eccentric nuclei and intracytoplasmic lumina. Papanicolaou. $\times 40$.

Eccentric nuclei and occasional intracytoplasmic lumina with mucin droplets are characteristic. Cytologic atypia is insignificant (fig. 11). The monomorphic pattern and absence of ME cells are key features to differentiate it from benign breast lesions. The clinical and radiologic findings and the gritty feel of the needle while aspirating are also helpful features [4–6].

ACC is rare ($<0.1\%$ of breast malignancies). It is often subareolar and well circumscribed, mimicking FA. The most defining features are the solid, homogeneous, acellular, cylindromatous spherules (most conspicuous as metachromatic and magenta on the Diff-Quick stain and gray-blue on the Papanicolaou stain). These are surrounded by 3-dimensional, uniform epithelial-cell clusters with scant cytoplasm, bland nuclei containing fine chromatin and scattered single cells similar to those in the clusters [97–100] (fig. 12). The cytologic differential diagnosis includes collagenous spherulosis, pleomorphic adenoma and metaplastic carcinoma (MC). Aspirates of collagenous spherulosis demonstrate amorphous hyaline globules, but the cells are arranged in 2-dimensional sheets with a lower N/C ratio and naked, bipolar nuclei are seen in the background. Aspirates of pleomorphic adenoma also contain metachromatic material, but this is more fibrillary with irregular feathery outlines compared to the metachromatic spheres of ACC. The cells are bland with ovoid and spindle nuclei. MC may have metachromatic stroma, but the cells show significant cytologic atypia not seen in ACC [97].

Fig. 12. FNA of ACC: homogeneous, cylindromatous, acellular spherules surrounded by uniform epithelial cell clusters with scant cytoplasm and bland nuclei. Diff-Quick. $\times 40$.

Mucinous Neoplasms and Lesions

Mucinous Carcinoma and Mucocele-Like Lesions

Aspirates of mucinous (colloid) carcinoma are usually cellular, consisting of monomorphic cells in an abundant extracellular mucinous background. The tumor cells may be arranged in 3-dimensional groups with smooth, rounded contours, monolayered sheets or as numerous isolated cells. They are generally uniform, bland-appearing with a wispy, microvesicular cytoplasm (fig. 13). The finding of diffuse cytoplasmic hyalinization with resulting eosinophilia has been described as characteristic of mucinous carcinoma. Their nuclei are eccentric, with uniform vesicular chromatin. Nuclear pleomorphism is minimal. Nucleoli are small and inconspicuous [101–105]. The finding of significant pleomorphism and necrosis indicates the presence of a mixed carcinoma. The background mucin has a stringy appearance that may have focal linear strands of filmy streaks or globes. It stains blue-green on Papanicolaou stain or bright pink on Diff-Quick. It can be highlighted by PAS, Giemsa or Alcian blue stains. Fibroblast and branching, thin-walled blood vessels are often included in the mucin [4–6].

Aspirates from mucocele-like lesions also yield abundant extracellular mucin. These lesions are hypocellular, however, and generally consist of flat sheets of cohesive epithelium and a few scattered histiocytes and fibroblasts. Unlike mucinous carcinoma, individual epithelial cells are rare or absent. Aspirates from mucinous carcinoma

Fig. 13. FNA of mucinous carcinoma: 3-dimensional groups of low-grade carcinoma cells in a mucinous background. Papanicolaou. $\times 40$.

that are very hypocellular and devoid of cytologic atypia or those associated with atypical ductal hyperplasia can be indistinguishable from mucocoele-like lesions. For all such aspirates, an interpretation of 'mucinous neoplasm or lesion' is appropriate and an excisional biopsy is recommended [6].

Mucinous carcinoma frequently simulates myxoid FA, clinically and cytologically. FAs generally occur in younger patients than do mucinous adenocarcinoma. Unlike mucinous carcinoma, FA demonstrates the presence of stroma, staghorn groups of ductal epithelium and ME cell components (numerous bare, bland, bipolar nuclei in the background).

Papillary Neoplasms

Intraductal Papilloma and Intracystic Papillary Carcinoma

Intraductal papillomas share many of the features of benign lesions of the breast, but their characteristic cytologic/histologic feature is the arborescent papillary growth of epithelial cells surrounding a fibrovascular core [106–109]. Despite this definition, a number of potential issues arise when dealing with a seemingly papillary proliferation on FNA. First, a papillary-like architecture can be seen in a number of benign and malignant nonpapillary proliferations. In their study, Simsir et al. [106] were able to confirm the diagnosis of true papillary prolifera-

tion in only 31 of 70 FNAs diagnosed as papillary neoplasms. The cases that were misdiagnosed varied from FA to DCIS to invasive ductal carcinoma. The features they found to be most helpful in clarifying this differential were: smear cellularity, nuclear pleomorphism and the presence of cytologically bland, columnar cells. Still, some cases failed a clear-cut distinction and categorization even after retrospective review. According to Michael and Buschmann [107], distinguishing true papillary from papillary-like proliferations is possible when the cytopathologist pays close attention to the presence of true fibrovascular cores covered by columnar cells and to large sheets with ruffled borders and small tongue-like projections, rather than bulbous and architecturally complex epithelial fragments with finger-like projections without true fibrovascular cores. One additional feature this paper described was the relative abundance of ME, naked nuclei in FAs relative to papillary tumors, and the complete absence of apocrine metaplasia in carcinomas as opposed to benign papillomas. Other papers have highlighted another element of potential confusion, namely the occasional infarction of papillomas and the resultant potentially significant reactive atypia [108, 109]. The presence of ghost cells, infarcted papillary fragments, degenerate columnar cells, extensive necrosis and squamous metaplasia may be helpful in such cases. Our stance towards papillary lesions is one compatible with the cautious attitude facing a diagnosis of intraductal papilloma on CNB, and emphasizes the need for surgical excision. Distinguishing a true papillary lesion from FA is probably the more relevant issue, and should be possible in the majority of cases, in order to avert an unneeded surgical excision.

Distinguishing a benign from an atypical/malignant papillary proliferation is an area of much contention, given the significant overlap in cytologic features [110, 111]. The most frequently quoted differential features favoring malignancy are: high cellularity, thin, single fibrovascular cores and complex branching patterns, discohesive cells with variable degrees of cytologic atypia (fig. 14b) and the absence of bland, bipolar and benign apocrine cells in the background [108, 112]. Despite the presence of helpful features favoring benign versus atypical/malignant papillary lesions, no single feature is pathognomonic for one entity versus another. In our experience, we have encountered cases with numerous, background, oval, naked nuclei compellingly suggestive of ME cells in papillary lesions with mildly atypical features that showed papillary carcinoma on follow-up surgical excision. We therefore maintain that the presence of a credible papillary pattern on cytology should prompt further intervention, either

Fig. 14. FNA of papillary lesions. **a** Fibrovascular cores forming true papillae. Papanicolaou. $\times 40$. **b** Discohesive low-grade tumor cells with intact cytoplasm in a case of intracystic papillary carcinoma. Papanicolaou. $\times 40$.

CNB or formal surgical excision. Correlation of the cytologic findings with clinical and radiographic information should also facilitate management decisions.

Benign and Malignant Spindle-Cell Lesions

Myofibroblastoma, Fibromatosis, MC and Malignant PT

Though rare, spindle-cell lesions of the breast comprise a large number of entities, spanning reactive to benign to locally aggressive and frankly malignant proliferations. Despite the divergent biologic behaviors of different tumors, cytomorphologic overlap is often significant, and any attempts at definitive classification of spindle-cell lesions based on cytology alone should be met with a healthy degree of skepticism [113]. The benign spindle-cell lesion most likely to lend itself to an accurate diagnosis is myofibroblastoma in its classic form. Myofibroblastoma's most salient features include oval-shaped discohesive tumor cells with evenly dispersed chromatin, inconspicuous nucleoli, mild pleomorphism, occasional nuclear grooves and intranuclear cytoplasmic pseudoinclusions and collagenous bundles [114]. Myofibroblastoma can, however, show a wide variety of morphologies and may exhibit high cellularity, marked pleomorphism, epithelioid morphology and mucinous stromal change, significantly complicating its cytologic diagnosis [115]. Other complicating factors in the diagnosis of benign spindle-cell tumors is the minimal atypia and low cellu-

larity present in potentially aggressive/malignant neoplasms such as fibromatosis and fibromatosis-like MC. A peculiar reactive mesenchymal tumor seen following invasive procedures is the postoperative spindle-cell nodule [116]. Because of their high cellularity and proliferative activity, these lesions can be worrisome on cytology. Knowledge of the clinical circumstances, namely prior manipulation and rapid unexplained growth, paired with the absence of significant hyperchromasia and nuclear irregularity and a conspicuous inflammatory and hemosiderotic background can assist the pathologist in rendering a correct benign diagnosis [117]. We reemphasize the extreme caution pathologists should exercise when dealing with mammary spindle-cell lesions. In cases where an adequate cell block is available, cytokeratin and p63 (for MC), desmin and CD34 (for myofibroblastoma) can be invaluable in establishing or excluding a specific diagnosis.

Highly atypical spindle-cell tumors generally pose little diagnostic challenges, and a diagnosis of malignant spindle-cell neoplasm can be readily made. The exact nature of the malignant spindle-cell neoplasm will, however, often defy more precise classification, especially without the assistance of histology and immunohistochemical evaluation. While primary breast sarcomas are exceedingly rare, malignant PTs with stromal overgrowth and metaplastic spindle-cell carcinoma represent the most common malignant spindle-cell lesions of the breast. The presence of a conspicuous, benign (albeit proliferative), epithelial component would favor a PT, while a biphasic

Fig. 15. FNA of florid gynecomastia: cellular smears with fragments of hyperplastic duct epithelium. Papanicolaou. $\times 40$.

epithelial/mesenchymal phenotype or the presence of malignant squamous differentiation would favor a MC [118–120]. When dealing with a purely sarcomatoid proliferation, the distinction between PT, MC or primary mammary sarcoma becomes immaterial as all three neoplasms mandate wide surgical excision without the need for axillary lymph node dissection in the absence of a clinically positive axilla [121].

Breast Masses in Males

Male breast masses are uncommon. The vast majority are benign (gynecomastia), while a few (5–12%) are due to either primary or metastatic malignancies. Florid gynecomastia has been the cause of false-suspicious and FP cases in the cytology literature [122, 130]. It is characterized by epithelial hyperplasia, both flat and micropapillary, often associated with ME cell proliferation and increased stromal cellularity (fig. 15). The fibrous/inactive phase of gynecomastia occurs later, has less epithelial hyperplasia and increased stromal collagen and is therefore less problematic on FNAs. FNAC of gynecomastia has been described as having hypocellular-to-moderately-cellular smears, cohesive sheets of bland duct cells, scattered ME cells and few spindle cells. Duct epithelial atypia (nuclear enlargement, overlap, pleomorphism or mitotic figures) is seen in up to one quarter of cases and, rarely, may be so severe that malignancy cannot be ruled out. Epithelial atypia is exaggerated with chemotherapy and radio-

therapy and anabolic drug abuse [127, 128]. FNAC of male breast carcinoma, on the other hand, is identical to its female counterpart. Florid duct hyperplasia and atypia seen in gynecomastia necessitate a higher threshold for cytologic interpretation of malignancy in males [126]. Helpful distinguishing features are cohesiveness of cells, a lack of single malignant cells, the absence of macronuclei and the presence of ME cells in florid gynecomastia. A detailed clinical history including drug and radiation therapy is helpful. In some aspirates, however, the distinction between benign and malignant cannot be made and a C3 or C4 diagnosis is unavoidable. Clinical correlation and/or biopsy should be recommended.

Conclusion

Inconclusive and erroneous FNAs of breast due to the ‘true gray zone’ are rare. The majority are due to overlapping cytologic features of some of the benign and malignant conditions we have described. The rest are due to rare conditions not necessarily familiar to practising pathologists. We described the FNAC of the common and rare lesions, pointing out the features that may help pathologists attain the correct diagnoses.

The original data from AUBMC was exempt from the local institutional review board. It was considered QI/QA data.

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