CONTINUING MEDICAL EDUCATION

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Challenging Breast Lesions:
Pitfalls and Limitations of Fine-Needle Aspiration and the Role of Core Biopsy in Specific Lesions

Aylin Simsir, M.D.* and Joan Cangiarella, M.D.

Core biopsy rapidly replaced fine needle aspiration (FNA) over the past decade in evaluation of diseases of the female breast in many centers in the USA. We continue to heavily utilize FNA for the initial evaluation of breast masses in our institution. In this article, we discuss the cytologic and core biopsy findings in challenging breast lesions such as papillary and mucinous proliferations, fibroepithelial neoplasms, and low grade cancers. We specifically focus on the pitfalls and limitations of both diagnostic modalities in these selected specific lesions. Diagn. Cytopathol. 2012;40:262–272.

Key Words: breast FNA; core biopsy; challenging lesions

The increase in core biopsy over the past decade has led to the demise of breast fine-needle aspiration (FNA) in many centers. For some lesions, core biopsy clearly has its advantages, but, in some settings, the use of FNA is equally as accurate with less cost and complications. In this article, we review a challenging group of breast lesions, including papillary lesions, mucinous lesions, fibroepithelial lesions, and low grade cancers, highlighting the pitfalls and limitations to their diagnosis by FNA and the role of core biopsy in specific lesions.

Papillary Lesions

Papillary lesions of the breast are uncommon and account for less than 5% of all breast lesions and ~2% of all carcinomas of the breast.[1,2] Papillary lesions represent a varied group of lesions ranging from benign papillomas to invasive papillary carcinomas.

In 1996, practice guidelines referred to as the "Uniform Approach to Breast Fine Needle Aspiration Biopsy" were published.[3] In these guidelines, papillary lesions were placed into an atypical/indeterminate category with definitive diagnosis deferred to histologic examination unless unequivocal features of malignancy were present. The problems encountered in the use of FNA for diagnosis of papillary lesions are distinguishing between benign and malignant papillary lesions and separating papillary neoplasms from nonpapillary lesions that show a papillary pattern on FNA.

Although distinguishing benign from malignant papillary lesions can be diagnostically challenging, several studies show that there are characteristic features that can separate these groups.[4–7] Papillomas yield cellular smears with complex and/or papillary fragments, which may or may not contain true fibrovascular cores; numerous bland appearing columnar cells in a cystic background containing macrophages (foam cells) and apocrine cells are characteristic (Fig. 1). Cellular dyshesion with single columnar cells is common (Fig. 2). In comparison, papillary carcinomas show more complex branching papillary fragments, small rounded clusters of cells, and numerous single cells, some of which are plasmacytoid and others that are columnar. Atypia is variable and bare oval nuclei are absent from the background. In comparison with papillomas, papillary carcinomas often show more cellularity, more dyshesion, and lack macrophages (foam cells) and apocrine cells in the background. A recent study reported stellate or meshwork tissue fragments to be a diagnostic feature of a papilloma.[8] Fibrovascular cores are reported to be seen more commonly in papillary carcinomas when compared with

New York University School of Medicine, Department of Pathology, New York, New York

*Correspondence to: Aylin Simsir, M.D., NYU Medical Center, 530 First Avenue, Skirball West Tower, Suite 10-U, New York, NY 10016. E-mail: aylin.simsir@nyumc.org

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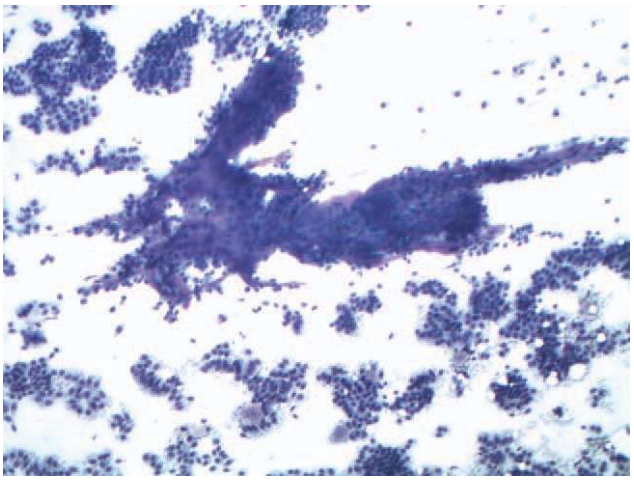

Fig. 1. Intraductal papilloma: Cellular sample showing a fibrovascular core in the center surrounded by epithelial cells; small and large clusters of epithelial cells are seen in the background (Diff-Quik, ×10). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

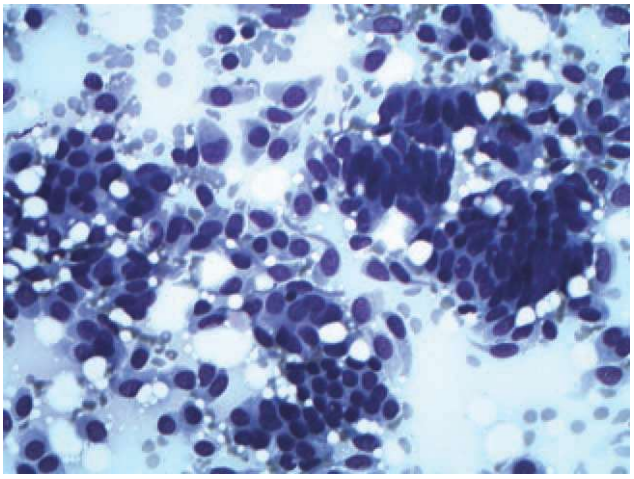

Fig. 2. Intraductal papilloma: High power of the same papilloma displays significant dissociation of cells, many columnar cells and a few plasmacytoid cells raising concern for carcinoma (Diff-Quik, ×40). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

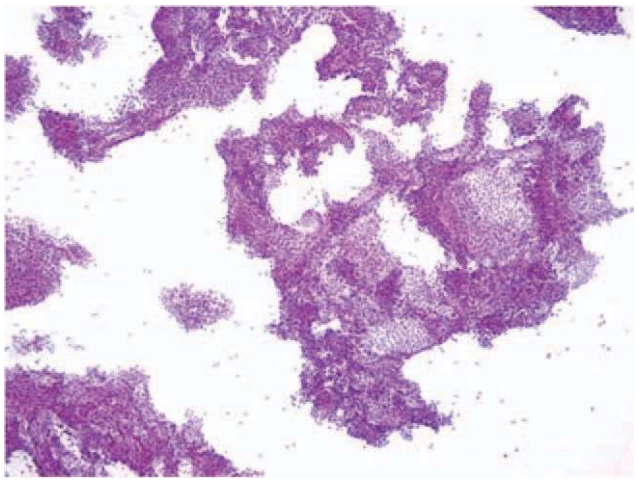

Fig. 3. Intracystic papillary carcinoma: Cellular sample showing many large complex branching clusters of epithelial cells, one in the center with a fibrovascular core (Papanicolaou, ×10). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

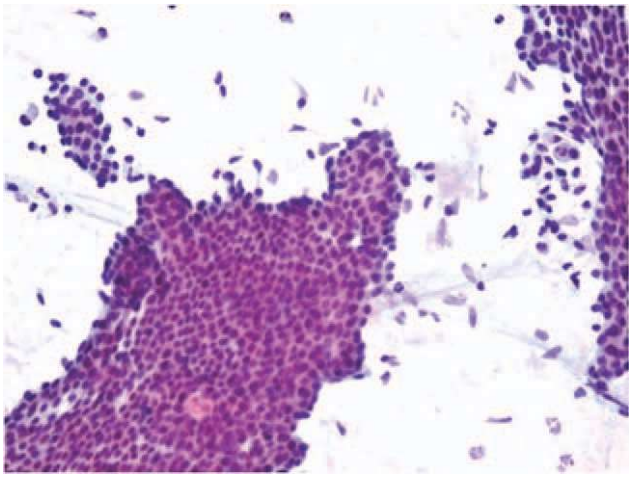

Fig. 4. Intracystic papillary carcinoma: Higher power reveals some dissociated columnar cells, and lack of oval bare nuclei; cytologic atypia is minimal. It is difficult to diagnose this case as carcinoma when compared to Figs. 1 and 2. (Papanicolaou, ×20). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

intraductal papillomas.[9] In our experience, despite all the described features above, distinction of benign versus malignant papillary lesions on cytology is nearly impossible (Figs. 3 and 4).

Summary of Characteristic Features of Benign Papillary Lesion on FNA

- Highly cellular smears
- Complex epithelial fragments with folding/branching
- True fibrovascular cores lines by epithelial cells
- Dispersed single columnar cells
- Variable epithelial atypia
- Background containing macrophages, cyst fluid and oval bare nuclei/bipolar cells (variable)

Distinguishing other lesions that show a papillary pattern on FNA is equally problematic. In our series, of 70 cases, we classified as papillary lesion on FNA, more than half were not true papillary lesions on surgical excision with 25% diagnosed as fibroadenomas or fibrocystic change.[4] Some cases of DCIS also appeared papillary on FNA. Distinguishing fibroadenoma and fibrocystic change from papillary lesions is important as management differs. Fibroadenomas typically contain numerous bare oval

nuclei, stromal fragments, and lack fibrovascular cores and single columnar cells distinguishing them from papillomas. Fibrocystic change generally lacks fibrovascular cores and while single columnar cells may be seen they are present in lower quantity than in papillomas.

The diagnosis of papillary lesions by core biopsy is also challenging due to the limited material obtained, fragmentation of the core pieces, presence of focal atypia due to sampling, and at times the inability to distinguish benign from atypical or malignant papillary lesions due to overlapping histologic features. Masood et al.[10] compared core biopsy to FNA in the diagnosis of papillary lesions and found the overall accuracy of FNA to be superior to core biopsy in distinguishing benign and malignant papillary breast lesions. Valdes et al.[11] found that papillary lesions diagnosed by stereotaxic vacuum assisted biopsy were less likely to be associated with malignancy at excision than papillary lesions diagnosed by FNA.

The literature shows that papillary lesions with atypia on core biopsy must be removed as a significant percentage, up to 67% of atypical lesions in one series show malignancy at surgical excision.[12] A greater controversy exists for benign papillomas diagnosed by core biopsy where the need for subsequent surgical excision remains controversial. Surgical excision of benign papillomas diagnosed by core biopsy shows no evidence of malignancy in some series[13,14] but rates of malignancy of up to 25% in others.[13] Although histologic features such as a monotonous population of epithelial cells with a solid and cribriform architecture, necrosis, cytologic atypia, and a lack of myoepithelial cells are predictors of carcinoma they can also be seen in atypical papillomas.[15] Immunohistochemistry for myoepithelial cells, such as p63 and calponin, can be used to distinguish papillomas from papillary carcinomas by illustrating the lack of myoepithelial cells in papillary carcinoma. Immunoreactivity with cytokeratin 5/6, cytokeratin 14, and 34BE12 is higher in papillomas when compared with papillary carcinomas.[16] Immunohistochemical staining with calponin, p63, and cytokeratin 5/6 has been shown to increase the accuracy of diagnosis of benign papillary lesions in breast core biopsy specimens compared to hematoxylin and eosin staining alone.[17] Even with immunohistochemistry, the accuracy in the diagnosis of benign papillomas by core biopsy is not 100% and thus most falter to recommend excision for complete evaluation.

In summary, the definitive classification of a papillary lesion is difficult by both FNA and by core biopsy. However, both methods can classify lesions as "papillary" thus guiding treatment and warranting excision.

Mucinous Lesions

The presence of mucin can be seen in a variety of breast lesions from fibrocystic change to mucocele-like lesion to colloid carcinoma.

Common Differential Diagnosis of Lesions Containing Mucinous Material on FNA

- Fibrocystic change
- Myxoid fibroadenoma
- Mucocele-like lesion
- Mucinous (colloid) carcinoma

On FNA, mucinous lesions can be separated into two categories: those that are colloid carcinomas and those that are not.[18] A diagnosis of colloid carcinoma by FNA can be made in the majority of cases and lead to definitive surgical management.[19] Colloid carcinoma shows moderate to markedly cellular smears containing epithelial cells with mild to moderate atypia in either three dimensional clusters, sheets, or singly in a background of abundant mucin (Fig. 5). A distinct cytologic feature is the presence of thin-walled capillaries free-floating or coursing through mucin (Fig. 6).[18]

Most other mucinous lesions seen on FNA will be due to fibrocystic change and myxoid fibroadenoma, with an occasional mucocele-like lesion. The presence of bare oval nuclei can help to distinguish fibrocystic change from colloid carcinoma. Fibroadenomas can be distinguished from colloid carcinoma by the presence of bare oval nuclei and stromal fragments (Fig. 7). Occasional problematic cases are those FNAs that are acellular or paucicellular and mucin rich; this type of aspirate may be seen in both fibrocystic change and mucocele-like lesion. Because mucocele-like lesion can be associated with DCIS and invasive carcinoma,[20] we recommend surgical excision in these rare cases as there are no definitive clinical or radiologic features that can distinguish a benign mucocele from that associated with DCIS or invasive carcinoma (Table I).[18]

Most mucinous lesions can be accurately classified by FNA, findings similar to those noted on core biopsy.[21,22] There are a few series that have studied mucinous lesions on core biopsy.[22–24] The majority feel that mucinous lesions can be accurately diagnosed by core and that excision is not warranted for those that are benign. One report recommended excision for all mucocele-like lesions diagnosed by core regardless of the presence of atypia due to the finding of atypical ductal hyperplasia at excision in those diagnosed as mucocele-like lesion on core biopsy.[23]

In summary, the majority of mucinous lesions can be accurately diagnosed by FNA or core biopsy. The mucocele-like lesions remain problematic for both diagnostic methods, and conservative excision should be recommended at this time to avoid missing a carcinoma at excision.

Fibroepithelial Lesions

Fibroadenoma

Fibroadenoma is one of the most common breast lesions to be referred for FNA. FNA is considered to be highly

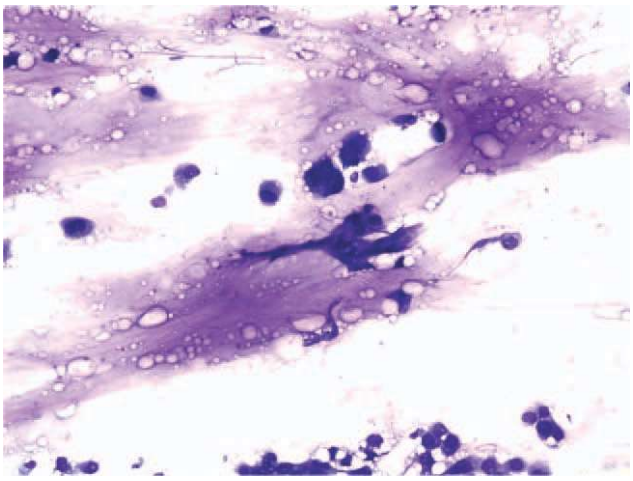

Fig. 5. Colloid carcinoma: Atypical epithelial cells singly and in clusters in a mucinous background (Diff-Quik, ×40). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

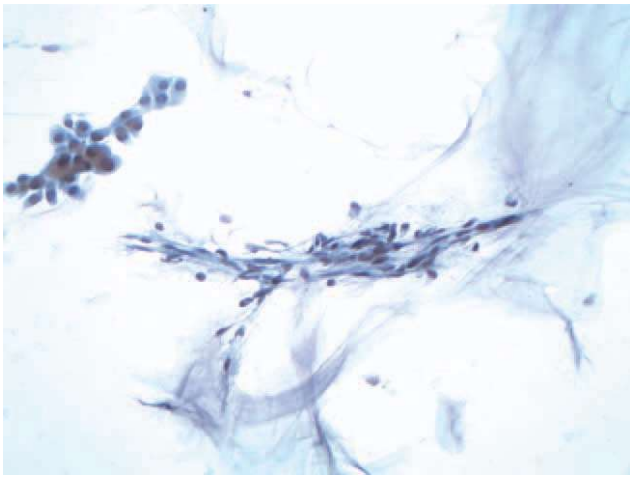

Fig. 6. Colloid carcinoma: Low cellularity, mild atypia, abundant mucin in the background and a free floating vascular structure in the center define this lesion as colloid carcinoma (Papanicolaou, ×20). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

reliable in the diagnosis of fibroadenoma.[25] The cytologic diagnosis of fibroadenoma is straightforward when typical features are present; cellular smears, with large branched (staghorn) monolayered sheets of uniform ductal cells intermixed with myopeithelial cells in a background containing oval bare nuclei and stromal fragments. It is not unusual to have single dissociated intact cells and atypia in the form of nuclear pleomorphism and enlargement and prominence of nucleoli in aspirates of fibroadenoma. Combined with cellularity of the smears, these features may be alarming and result in a false suspicion for carcinoma.[26–28] Similarly, there are breast carcinomas that may closely mimic fibroadenoma on FNA.[28,29]

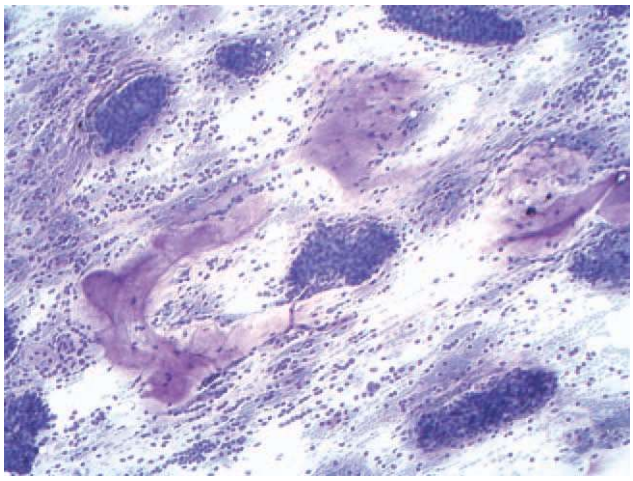

Fig. 7. Myxoid fibroadenoma. Myxoid stromal fragments, and small and large clusters of epithelial cells are seen in the background of abundant mucinous material stromal fragments and oval bare nuclei. (Diff-Quik, ×20). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Table I. Summary of Differential Cytologic Findings in Lesions with Extracellular Mucinous Material on FNA

Entity	*Cytologic features*
Fibrocystic change	Variable cellularity
	No stromal fragments
	Myopeithelial cells
	Macrophages
	Apocrine cells
	Mucicarmine (+)
Myxoid FA	Myxoid stromal fragments
	Staghorn epithelial clusters
	Oval bare nuclei (numerous)
	Mucicarmine (−)
Mucocele like lesion, benign	Acellular or sparsely cellular smears
	Myoepithelial cells
	No atypia
	Mucicarmine (+)
Mucocele like lesion, malignant	Increased cellularity
	Mild to moderate atypia
	Single cells
	Mucicarmine (+)
Colloid carcinoma	Increased cellularity
	Mild to moderate atypia
	Single cells floating in mucin
	Vascular structures
	Mucicarmine (+)

The great majority of fibrodenomas with atypia on FNA are confirmed to be conventional or myxoid fibroadenomas on excision. They usually display benign cytologic atypia attributed to hormonal stimulation, lactational change, secretory and apocrine metaplastic changes, and/or response to inflammation.[26] These changes are recognized as a variation of normal by the surgical pathologist and not reported to the surgeon in the final report as they carry no clinical consequence. Other fibroadenomas may be more complex in nature and contain proliferative changes such as marked ductal

Table II. Summary of Comparative Cytologic Features of Fibroadenoma and Phyllodes Tumor

	Fibroadenoma	*Phyllodes tumor*
Stromal fragments	Small and hypocellular	Large and hypercellular
Epithelial fragments	Branching, staghorn	Broad, rounded
Epithelial/stromal ratio	Low	High
Background myoepithelial cells	Oval bare nuclei	Spindled and plump cells with retained cytoplasm in the background; atypia (prominent nucleoli and pleomorphism) present in high-grade PT

hyperplasia, apocrine cysts with or without hyperplasia, and sclerosing adenosis that may lead to atypia and dissociation of cells on aspiration. It is important to remember that if the overall cytologic pattern supports a diagnosis of fibroadenoma, one should exercise caution in evaluating atypia and refrain from overcalling such lesions. Conversely, there is the potential for underdiagnosing breast carcinoma as fibroadenoma. In our experience, breast carcinomas that mimic fibroadenomas are usually intraductal or well differentiated and grow in nests in a fibrotic/desmoplastic stroma; in these cases, the stroma can be mistaken for the stromal fragments seen in fibroadenoma, and the naked tumor nuclei in the background resemble the oval bare nuclei of fibroadenoma. In these challenging cases, one very important clue is the presence of many single bipolar nuclei, which indicate a benign lesion whereas the complete absence, a malignant one.

On occasion, it may also be challenging to distinguish myxoid fiboradenoma from colloid carcinoma.[30–32] Abundant extracellular mucinous material and dissociated single epithelial cells in myxoid fibroadenoma may lead to an atypical/suspicious or false-positive diagnosis. In addition, the lack of atypia or presence of minimal atypia displayed by the neoplastic cells in some colloid carcinomas and paucicellularity of samples may blur the picture. Close attention to the bimodal nature of the cell population in myxoid fibroadenoma, epithelial cells admixed with stromal fragments and oval bare nuclei, should secure a correct diagnosis.

It seems obvious that in such difficult cases, the triple approach combining clinical, radiologic, and cytologic findings is essential. Nevertheless, in some cases, a definitive diagnosis may not be possible, and the patient will be referred for core biopsy or excision. It is important to mention that similar problems, although less frequently may be encountered in core biopsy. For example, Rosen states that sclerosing adenosis as a component of complex fibroadenoma may be a source of a false-positive diagnosis of invasive carcinoma on core biopsy.[33] Extreme stromal myxoid change in a fibroadenoma may displace the epithelial component into compressed slender cords and result in a false-positive diagnosis of colloid carcinoma.[33]

Fibroadenoma Versus Benign/Low-Grade Phyllodes Tumor

Phyllodes tumor (PT) is a biphasic epithelial/stromal neoplasm of the breast. In contrast to fibroadenoma, PT is a rare tumor comprising less than 1% of all breast tumors. FNA can accurately diagnose malignant PTs in most cases. On the benign/borderline end of the spectrum, cytologic features of fibroadenoma and PT overlap making FNA diagnosis difficult. Precise preoperative distinction is important for optimal patient management. Fibroadenomas are cured by simple enucleation whereas benign and low grade PTs require wider excision with clean margins to prevent local recurrence. Classic cytologic features in PT are similar to fibroadenoma. However, in contrast to fibroadenoma, stromal fragments are larger, increased in number (stromal overgrowth), and are hypercellular (phyllodes fragments), and the single stromal cells in the background are plumper than the typical oval bare nuclei seen in fibroadenoma (Fig. 9). These single cells are intact spindled cells with retained cytoplasm (not naked nuclei) and show variable degrees of nuclear atypia with nucleoli and pleomorphism (Table II).

However, some of these features may be entirely lacking in benign and low grade PTs even after retrospective review of smears making their differentiation from fibroadenoma virtually impossible. It is not surprising that a considerable portion of benign and low grade PTs is initially diagnosed as fibroadenoma on cytology.[34–37] This in part reflects sampling problems as hypo- and hypercellular areas tend to alternate within PTs. Another important diagnostic pitfall in PTs is the presence of a significant epithelial proliferation including atypical ductal epithelial hyperplasia. If these areas are sampled by FNA, this may lead to a false-positive diagnosis of an epithelial lesion/neoplasm. We encountered this problem even with high-grade (malignant) PTs; one case required core biopsy due to inability of FNA to rule out an atypical papillary lesion.

Core biopsy in PTs is also problematic. A definitive diagnosis of PTs is rarely made on core biopsy. It is especially difficult to differentiate cellular fibroadenoma from benign/low grade PT. In comparison, in one study, the possibility of PT was raised in 23% of cases on FNA and 65% on core biopsy.[38] In two others, 11 of 44 (25%) and

9 of 23 (39%) surgically resected PTs were reported as fibroadenoma or other benign lesion on core biopsy.[39,40] Similar to FNA, some PTs are diagnosed as fibroadenoma on core biopsy due to tumor heterogeneity. Histologic features that are more common in core biopsy from PT when compared with fibroadenoma include increased stromal cellularity, stromal overgrowth (10X field with no epithelium), fragmentation of the cores, and adipose tissue within stroma.[39] Similar to FNA, some PTs are diagnosed as fibroadenoma on core biopsy due to tumor heterogeneity.

Low Grade Cancers

Intraductal Adenocarcinoma

FNA diagnosis of DCIS poses two issues. (1) Diagnosis of low grade DCIS is difficult due to mild atypia associated with this lesion. (2) Diagnosis of high-grade DCIS is usually straightforward, but its distinction from invasive carcinoma is impossible.

Cytologic features of low grade DCIS include cellular smears with cohesive three-dimensional sheets or papillary clusters of cells arranged around a central lumen creating a cribriform pattern (Fig. 8). The sparsity of dispersed single cells and minimal degree of cytologic atypia contribute to the difficulty in diagnosis.[41–43] Distinguishing low grade DCIS from atypical hyperplasia may be impossible. Atypical ductal hyperplasia shows cohesive monolayered sheets or tight clusters of ductal epithelial cells with less nuclear atypia when compared with cases of DCIS. Diagnosis of high-grade DCIS is straightforward, because these lesions usually yield highly cellular smears with three-dimensional groups of large pleomorphic cells, dissociated single malignant cells, and an absence of myoepithelial cells.[44] Necrosis and calcific debris are common. A major pitfall is the difficulty in distinguishing high-grade DCIS from invasive carcinoma on aspiration biopsy.[45–48] Key cytologic features that can be used to predict invasion include malignant cell clusters forming tubules, single tumor cells with intracytoplasmic lumina, fibroblastic proliferation, the presence of fragments of elastoid stroma, and the infiltration of malignant cells into fat or stroma. Problems occur with overlapping features as infiltration of fibrofatty stroma by tumor cells have been described in in situ lesions. In our practice, we do not differentiate in situ from invasive carcinoma on FNA. Although there are advocates of making this distinction on cytology, the literature is not supportive of FNA being reliable in making this distinction. For example, McKee et al.[47] studied 66 invasive and 14 in situ carcinomas of breast with histologic follow-up. They found six features that showed a statistically significant difference between invasive and in situ cases. These were infiltration of fat or stroma by malignant cells (72% of invasive cases demonstrated this feature, not present in any of the in situ cases), the presence of myoepithelial cells overlying clusters of tumor cells (seen in 86% of in situ tumors and 7% of invasive cases), calcification (present in 71% of in situ and 15% of the invasive group), foamy macrophages (noted in 64% of in situ tumors and 16% of invasive carcinomas), intracytoplasmic vacuoles (seen in 50% of invasive cases and 21% of in situ lesions), and tubules (present in 30% of invasive and 7% of in situ tumors). They concluded that invasion can be suggested in FNA of carcinomas, provided that true infiltration of fibrofatty connective tissue by neoplastic cells is present. However, they did comment that despite in situ disease having its characteristic features, the presence of invasion cannot be excluded even in the presence of stromal or adipose tissue fragments without tumor infiltration. Wang et al.[49] studied cytomorphologic features in 16 FNAs from biopsy-proven DCIS and 39 FNAs from invasive ductal carcinomas. They concluded that although the suspicion of DCIS might be raised when hypocellularity, benign epithelial cells, and macrophages are noted in a FNA of the breast that has positive results or causes suspicion for malignancy, FNA cannot reliably distinguish DCIS from infiltrating ductal carcinoma.[49] Sneige et al.[46] concluded that tubular structures of tumor cells and the presence of stromal fragments in breast FNA are significant indicators of stromal invasion. However, the low occurrence rate of tubular structures (24% in their series) in invasive carcinoma and the low specificity of stromal fragments limited their utility in separating invasive carcinoma from DCIS.

Problems exist for core biopsy where the distinction of atypical ductal hyperplasia from low grade DCIS can be problematic, and a certain percentage of cases diagnosed as DCIS only on core biopsy will have invasive carcinoma at excision. The discussion of ADH versus low grade DCIS, well known to every surgical pathologist, is beyond the scope of this review. A very brief discussion of invasive cancer after a diagnosis of DCIS on core biopsy to highlight this problem is as follows: Dillon et al.[50] reported invasive carcinoma in 33% patients and microinvasion in 14% patients whose core biopsy showed DCIS. A preoperative finding of calcification only on mammogram was associated with DCIS on excision whereas the presence of other mammographic features increased the risk of invasion. A size of equal to or greater than 5 cm on excision was also associated with an increased risk of invasion. Meijnen et al.[51] studied the risk of invasion and axillary lymph node metastasis in patients with DCIS diagnosed by preoperative core biopsy. Of 172 DCIS lesions diagnosed by core biopsy, invasive carcinoma was found in the surgical specimens in 45 tumors (26%). Risk factors for invasion were presence of a palpable lesion, presence of a mass on mammography, and intermediate or high-tumor nuclear grade.

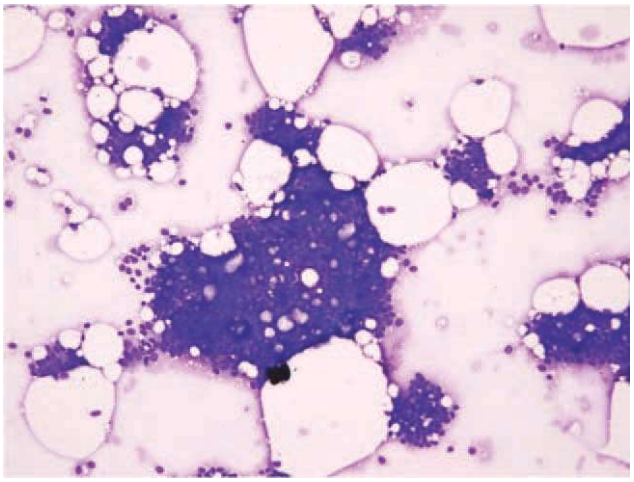

Fig. 8. Low grade DCIS. Small and large clusters of epithelial cells, in the center showing punched out holes-(cribriform pattern) low grade cytologic atypia and dissociated smaller groups and single cells (Diff-Quik, ×20). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

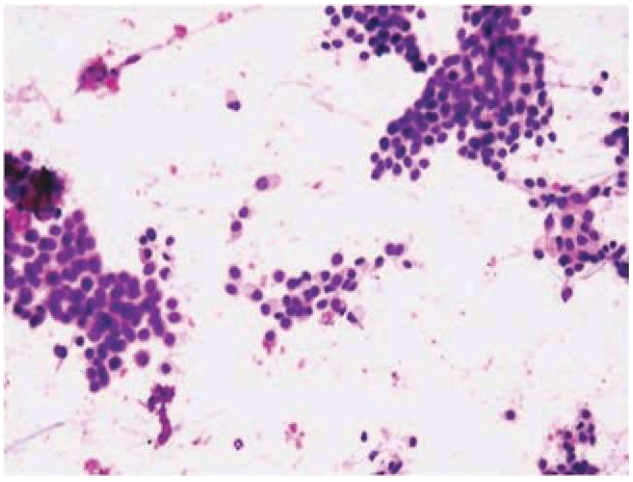

Fig. 9. Invasive lobular carcinoma. Moderately cellular smear showing clusters of small cells- background lacks oval bare nuclei. In the center, dissociation of cells with plasmacytoid features and a few cells displaying intracytoplasmic vacuoles are seen. Cellular atypia is mild. (H&E, ×40). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Lobular Carcinoma

Lobular carcinoma is associated with the highest false-negative rate among all types of mammary cancers.[52–60] The high-false-negative rate is due to several factors including paucity of cells, small cell size, and subtle cytologic atypia all of which may lead to interpretive error. In a study by our group, our false-negative rate was 4%.[60] Errors were either interpretational or due to sampling. Others have found much higher false-negative rates in their practice and recommended core biopsy when lobular carcinoma is suspected. Sadler et al.[58] reviewed the method of diagnosis in 56 patients with lobular carcinoma who had attended screening and symptomatic clinics. In only 52% of patients, FNA was diagnostic of malignancy; the mean tumor size was 21 mm. In 48% of patients, FNA failed to demonstrate malignant cells; the mean tumor size in this group was 23 mm. Ten patients were diagnosed by needle-core biopsy when FNA was not diagnostic.

In our experience, lobular carcinoma of classic histology is the main reason for false-negative or equivocal diagnoses on FNA; these tumors on FNA display mild atypia, low-to-moderate cellularity, and rare single cells (Fig. 9). Histologically, single files or small groups of tumor cells are embedded in and separated by abundant desmoplastic or fibrotic stroma. Positive cases are more often of the nonclassic types and show moderate to marked atypia and less desmoplasia and fibrosis in the histologic sections. We also note that smear cellularity does not correlate with the histologic cellularity of the tumor, but rather is a reflection of the architectural arrangement of the neoplastic cells; tumor cells that form epithelial groups/clusters, such as the alveolar, trabecular, and solid invasive lobular carcinomas yield more cellular

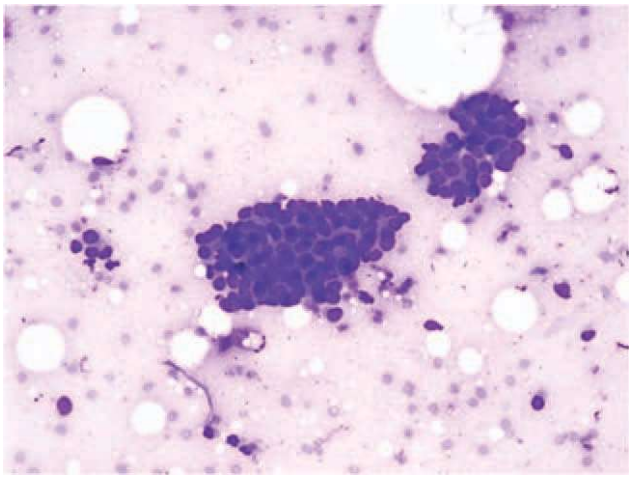

Fig. 10. Tubular carcinoma. Scantly cellular specimen- cluster in the center has a pointed end- a few single dissociated cells are noted; the background lacks oval bare nuclei (Diff-Quik, ×40). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

aspirates when compared with the classic type. Similarly, Abdulla et al.[61] noted that in the majority of cases of lobular carcinoma, cellular yield of FNA was disproportionately lower than expected when compared with the corresponding histocellularity. When the cytocellularity was moderate or high, the corresponding histocellularity always showed moderate or high cellularity. When the cytocellularity was low, the corresponding histology showed low histocellularity in only 6.3% of cases.[61]

In a certain percentage of classic lobular carcinomas, a definitive diagnosis of malignancy may be impossible by FNA. Core biopsy is advantageous in these cases. Histo-

logically, subtle invasive lobular carcinomas can be studied further by obtaining deeper levels and by application of immunohistochemical stains such as AE1/AE3 and CK 7, which will highlight the individual tumor cells.[59]

Tubular Carcinoma

The diagnosis of tubular carcinoma on FNA is challenging. A significant portion of cases of tubular carcinoma is given a negative diagnosis by FNA.[62–68] In one study comparing FNA and core biopsy in the diagnosis of tubular carcinoma, the sensitivity (for positive and suspicious diagnoses) of FNA was 50% and core biopsy was 91%.[62] Twenty-two percent of cases were given a benign diagnosis by FNA in comparison with 4.5% by core biopsy. In a FNA study done by our group, our false-negative rate was 14% with 45% of patients receiving a definitive "malignant" diagnosis and 36% receiving an "atypical" or "suspicious" diagnosis.[68]

The cytologic features of tubular carcinoma are moderately to highly cellular smears with monolayered sheets or angular cellular clusters displaying sharp borders, oval cells perpendicularly arranged along the edges of the clusters, and variable number of single tumor cells with minimal atypia (Fig. 10). Oval bare nuclei are usually absent but may be seen in some cases. Acellular fibrous or elastotic stroma can be seen in some cases. Differential diagnosis is broad and includes benign proliferative lesions such as fibrocystic changes, fibroadenoma, radial sclerosing lesion/radial scar, sclerosing adenosis, tubular adenoma, atypical ductal hyperplasia, and low-grade ductal carcinoma in situ. Among these, radial sclerosing lesions can be particularly problematic, because they can mimic tubular carcinoma mammographically presenting as a spiculate mass. Angular cell clusters can be seen in radial sclerosing lesion, but the smears are usually of lower cellularity and have more myoepithelial cells and fewer single ductal epithelial cells.[69] Sclerosing adenosis yields moderately to highly cellular smears with small acinar sheets, scattered dissociated individual epithelial cells, and small, dense, and hyalinized stroma; myopeithelial cells are present. Cellularity and dissociation of cells may lead to concern for malignancy.[70] Tubular adenomas can also show tubular arrangements of ductal epithelial cells or small spherical clusters of ductal epithelial cells but with abundant myoepithelial cells; these lesions are usually well circumscribed on imaging.[71] Fibrocystic change and fibroadenoma smears show monolayered sheets rather than sharply delineated angular clusters and have many more oval bare nuclei than tubular carcinoma.[68] When in doubt, core biopsy should be done. The main differential diagnosis on core biopsy includes complex sclerosing lesion/radial scar and sclerosing adenosis.[72,73] In difficult cases, immunohistochemistry is invaluable. Tubular carcinoma typically lacks a myoepithelial cell layer, which can be seen both in H&E sections as well as immunohistochemically by lack of staining with myopeithelial markers such as SMA and p63.[73]

Assessment of Molecular Markers

Although many studies showed reliability in the assessment of estrogen (ER) and progesterone (PR) receptors in cytologic material, considerable interlaboratory variability exists in the detection of hormone receptors and reporting of results in cytology.[74,75] Problems associated with the measurement of hormone receptors on cytology specimens include differences in the fixation method (air dried, alcohol-fixed, and formalin fixed), specimen preparation method (smear, cytospin, and cell block), the dilution and clones of the antibodies used, and the antigen retrieval process. These variables are also valid for her-2-neu immunocytochemistry (ICC). We do not routinely perform hormone receptor studies on cytologic specimens, unless a patient has metastatic disease in which we perform these markers on cell blocks with conditions similar to surgical specimens. If a laboratory chooses to perform prognostic marker studies on cytology specimens, validation and standardization of preanalytic and analytic methods must occur as well as participation in internal and external quality control programs. In addition, due to a lack of standardized methodology which affects reliability and accuracy for the ICC evaluation of Her-2-neu, the preferred method for assessment of her-2-neu on cytologic specimens is fluorescent in situ hybridization and not ICC.

The concordance rate between core biopsies and surgical specimens for the assessment of ER ranges from 86 to 98.8% and for PR ranges from 69 to 89%.[76] Because of the heterogeneity of staining, we have had an occasional case where there was discrepancy between the hormone receptors performed on core biopsy and surgical biopsy. The concordance rate between core biopsy and surgical biopsy for her-2-neu ranges between 60 and 96%.[76] Studies have shown more intense staining for her-2-neu in surgical specimens, which can influence therapeutic decisions.[76]

In our institution, we perform prognostic markers on core biopsies only in cases receiving neoadjuvant therapy or in metastatic disease.

Although there are only a few studies in the literature, it is our opinion that the utility of FNA specimens and core biopsies of the breast for genomic and proteomic profiling will increase in the next decade.

CME QUESTIONS

1. *Charateristic cytologic features of a benign papilloma includes all of the below EXCEPT*
   A. Highly cellular smears
   B. Complex epithelial fragments with folding/branching
   C. True fibrovascular cores lines by epithelial cells

D. Dispersed single columnar cells
E. Stromal fragments

Answer: E

2. *What is the most common entity entering the differential diagnosis of colloid carcinoma on FNA?*
   A. Radial scar
   B. Myxoid fibroadenoma
   C. Phyllodes tumor
   D. Atypical papilloma
   E. Myxoid liposarcoma

Answer: B

3. *Which feature below is helpful in distinguishing fibroadenoma and Phyllodes Tumor?*
   A. Overall cellularity of the smear
   B. Epithelial atypia
   C. Presence of stromal fragments
   D. Cellularity of the stromal fragments
   E. Cellular discohesion

Answer: D

4. *Which type of cancer below is associated with a high false-negative rate on FNA?*
   A. Tubular cancer
   B. High-grade DCIS
   C. Medullary carcinoma
   D. Colloid carcinoma
   E. Metastatic carcinoma to the breast

Answer: A

5. *Which factors below contribute to a false-negative diagnosis of lobular carcinoma on FNA?*
   A. Necrosis in tumor cells
   B. Mobile tumor mass causing difficulty in aspiration
   C. Overlapping cytologic features with myxoid fibroadenoma
   D. Presence of myoepithelial cells/oval bare nuclei
   E. Low cellular yield by FNA sampling

Answer: E

6. *In the diagnosis of papillary lesions which of the following is FALSE?*
   A. FNA can distinguish benign from malignant papillary lesions
   B. The cytologic features of papillary lesions on FNA can overlap with fibroadenomas and fibrocystic change
   C. Immunohistochemistry with calponin, p63 and cytokeratin 5/6 can increase the accuracy of diagnosis of papillary lesions
   D. Atypia seen on both core biopsy and fine needle aspiration warrants excision

Answer: A

7. *A mucicarmine stain is positive for mucin in all of the following except:*
   A. Colloid carcinoma
   B. Myxoid fibroadenoma
   C. Mucocele-like lesion
   D. Fibrocystic change

Answer: B

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