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Diagnostic Dilemmas and Pitfalls in ThinPrep® Cytology of Breast Fine Needle Aspiration Biopsy: report of 6 cases with histological correlates

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Abstract

Fine needle aspirations (FNA) of the breast for primary diagnoses have become less popular in the USA and are usually performed for lesions with low or extremely high clinical suspicion. They are also performed for lesions in close proximity to a breast implant. Liquid-based cytological preparations, such as ThinPrep® (TP), provide a practical alternative to clinicians who are performing FNA. Using a selection of cases that represent challenging diagnoses, we describe common diagnostic pitfalls of breast FNA that are specifically associated with this preparation. Well known breast cytology pitfalls, such as fibroadenoma, when solely examined using a TP slide can be even more challenging since the usual stripped bipolar cells seen in the background of smeared slides, can appear singly dispersed with preserved cytoplasm, resembling carcinoma. We describe that large fragments of solid papillary carcinoma are represented by mostly singly dispersed cells with plasmacytoid features that mimic those of a lobular carcinoma. Since nuclear features are more pronounced in TP, prominent nucleoli and cytological atypia can potentially be overcalled. TP processing might also lead to clumping of epithelioid histiocytes that appear atypical, which increases the suspicion of malignancy. The presence of atypical cells in a TP slide of a peri implant seroma should always undergo additional testing, especially in patients with a prior history of breast carcinoma, to determine if it represents recurrent carcinoma or an implant associated anaplastic large cell lymphoma. Familiarity with the aforementioned artifacts associated with TP is essential to avoid diagnostic misinterpretations.

Keywords

breast; cytology; ThinPrep; liquid based; pitfalls

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Introduction

The practice of fine needle aspiration (FNA) allows tissue sampling with minimally invasive procedures and is of great utility for cancer staging and management, such as in the pre-operative assessment of clinically suspicious lymph nodes and in the evaluation of metastatic sites or local recurrences.

The past two decades have witnessed a marked decrease in the use of diagnostic breast FNA.¹ The decline in the popularity of this technique can be attributed to multiple factors, including the inability to discriminate between invasive and in situ carcinoma in cytological specimens; the need for strict correlation with clinical and radiological findings (triple screening), which is not always feasible; and the numerous diagnostic pitfalls that could lead to false negative or false positive results. Nonetheless, FNA still has an important role in the work-up of non-suspicious breast lesions and more importantly in sampling of metastatic sites.² In our institution, FNA of the breast is currently used as a primary diagnostic method in rare cases in which there is either an extremely low or an extremely high suspicion of malignancy or when an imaging finding near an implant causes concern. Furthermore, it has been our observation that a positive primary diagnosis by FNA will almost always be confirmed with core needle biopsy before definitive surgery is performed.

Liquid-based cytology specimens such as ThinPrep® (Cytoc Corporation, Boxborough, MA, USA) have gained popularity mainly because bedside slide preparation is not required and liquid-based collection optimizes cell recovery.³ Studies have reported that the liquid-based technique ThinPrep® (TP) has a sensitivity and specificity of 86–100% and 74–98%, respectively, for the diagnosis of breast malignancies.^{3–5} The comparison of TP with conventional smears has led to the identification of an array of artifacts related to the TP technique that could potentially affect the diagnoses in different organ sites.^{3,6–8} Here, we aim to highlight common diagnostic pitfalls and challenges of breast FNA cases with TP slides.

Materials and Methods

We conducted a search for cytology breast specimens between 2011 and 2016 that were flagged for quality assurance in the cytology files at Memorial Sloan Kettering Cancer Center. These cases represented either discrepancies between the cytological and histological diagnoses or complex and educational cases. A subsequent matching histologic specimen was available for most cases.

The cytology specimens reviewed included direct smears, TPs, and cell block sections. Air-dried smears had been previously stained using a modified Romanowsky stain (Diff Quik), and alcohol-fixed smears and TP slides were stained with Hematoxylin and Eosin (H&E) and Papanicolaou (Pap) respectively. Subsequent histologic sections were 4 µm thick and were stained with H&E. Clinical and radiologic information was retrieved from our institution's electronic medical records.

Cytologic features on TP were evaluated and compared with the established criteria for cytologic diagnosis and with the subsequent final histologic diagnosis for each case, with the

exception of case 6, which did not have a matching histologic specimen. Cytologic features, diagnostic pitfalls on TP, and clinical-radiological characteristics of each case are discussed individually.

Case Reports and Discussion

We reviewed six breast FNA specimens from different patients with emphasis on the diagnostic features of each entity on the TP slide.

Fibroadenoma vs low grade carcinoma: Direct comparison between two cases

Case 1

A 51-year-old woman presented with a firm, palpable left breast mass. Ultrasound showed a solid, well-circumscribed mass with overall benign radiological features. The FNA specimen was hypercellular with variably sized epithelial cell clusters and numerous single cells. Focally, the epithelial clusters showed branching, crowding, and mild nuclear atypia. Background single cells appeared to be predominantly epithelioid with intact cytoplasm and only very rare stripped nuclei. The presence of well-preserved single cells on the TP slide invoked concern, and although the diagnosis of fibroadenoma was favored following correlation with ultrasound findings, a low grade ductal carcinoma was in the differential diagnosis. A subsequent excisional biopsy confirmed that the lesion was a 1.5 cm fibroadenoma. (Figure 1; A and B)

Fibroadenomas commonly lead to cytologic misinterpretation because of their morphologic similarity with other lesions, such as fibrocystic change, phyllodes tumor, and, most importantly, low-grade carcinoma. The classic triad of cytologic findings that characterize fibroadenomas are tight clusters of epithelial cells in a “staghorn-like” shape, background naked bipolar nuclei, and stromal fragments.² Even though this triad can sometimes be easily recognized, it might not be present in all cases.⁹ The abovementioned case is such an example; the rarity of naked bipolar nuclei and presence of numerous single epithelioid cells on TP was likely the reason for the initial consideration of malignancy.

It has been suggested that TP alters the classic cytological appearance of fibroadenomas, making the diagnosis of this entity cumbersome. Ly *et al.* observed marked hypercellularity and reduced number of background stripped nuclei in the TP samples compared to the cytopsin preparations of fibroadenomas.¹⁰ The homogenization step in TP, which is intended to disperse debris and promote a random distribution of cells, disrupts the cellular architecture and might be accountable for the reduction of epithelial clusters with staghorn configuration.¹⁰ Michael *et al.* suggested that stripped nuclei (myoepithelial cells) may be pulled through the TP filter during processing with a resulting reduction in their number.⁶ On the other hand, Biscotti *et al.* reported more abundant identifiable myoepithelial cells in aspirates of benign masses prepared by TP.³ Although the diagnosis of fibroadenoma is relatively simple when all the classic cytomorphologic features are present, it can be challenging if only a TP slide is available.

Case 2

An 85-year-old woman with a history of solid papillary ductal carcinoma of the left breast, status post excision and radiation therapy, presented with a contralateral breast mass and suspicious mammographic findings. An FNA was performed and the TP slide showed monomorphic dyshesive cells as well as cell clusters, leading to a positive adenocarcinoma diagnosis. Subsequent resection showed a low to intermediate grade ductal carcinoma in situ (DCIS). (Figure 1; C and D)

While this case does not represent a diagnostic discrepancy, it is presented here to highlight its similarities with Case 1 (fibroadenoma). Morphologic features suggesting ductal carcinoma over fibroadenoma include the presence of many more dyshesive atypical cells, which may or may not show significant pleomorphism, and the absence of naked bipolar nuclei (myoepithelial cell morphologic hallmarks).¹¹ TP preparation is associated with a decreased size of cell clusters, presence of more fragmented large branching sheets, and a higher number of single cells, resulting in apparent dyshesion.⁶

It has been shown that the diagnostic accuracy of the integrated evaluation of physical examination, mammogram, and FNA approaches 100%.^{7,8} For the specific purposes of differentiating in situ from invasive ductal carcinoma in the setting of a palpable breast mass, a cytology specimen yielding malignant cells is almost always invasive cancer (~98% of cases).¹¹ It is essential for the cytopathologist to be aware of the potential artifacts associated with TP processing, which can alter the cohesion of tumoral cells.

Not all plasmacytoid cells represent lobular carcinoma

Case 3

A 61-year-old woman with no prior history of malignancy presented with a palpable left breast mass and suspicious imaging findings. An FNA biopsy was performed and the TP slide showed numerous single cells with plasmacytoid morphology. The case was diagnosed as positive for carcinoma, with a high suspicion of a lobular phenotype. A subsequent segmental resection revealed an intermediate grade invasive ductal carcinoma with solid-papillary growth pattern. (Figure 1; E and F)

As discussed earlier, the homogenization step in TP processing results in the disruption of epithelial fragments/papillary clusters, leading to an artificial single cell pattern.^{6,7} In contrast, lymphocytes, which usually have a single cell presentation, tend to cluster in TP preparations.^{6,12} Invasive lobular carcinomas correspond to 5–15% of all invasive carcinomas.¹¹ The distinction of lobular from ductal carcinoma solely by cytological evaluation can be challenging.¹³ Features that favor the diagnosis of lobular carcinoma include single-file cellular groups, numerous poorly cohesive uniform and monomorphic single cells, small tumor cell size, minimal atypia, presence of intracytoplasmic mucin, and plasmacytoid appearance. However, none of these features is specific, and they can also be observed in ductal carcinomas.¹² The numerous isolated dyshesive plasmacytoid cells in the current case led to a suggestion of tumor type misdiagnosis of lobular carcinoma. While tumors with a solid-papillary growth pattern are composed of small cells with neuroendocrine features, TP preparations typically show artifactual dyshesive plasmacytoid

cells. Therefore, when evaluating a breast TP cytological specimen, it is imperative to consider that a dyshesive single cell pattern does not always represent a true morphological feature of the lesion, but that it might represent an artifact associated with TP processing.

Invasive lobular carcinomas, including those of large size, might not be palpable, and the associated mammographic abnormalities may be subtle.^{14,15} The FNA biopsy of lobular carcinoma might have low cellularity due to the characteristic associated fibrosis, and the tumor cells might be small, monomorphic, with minimal atypia. Overall, we suggest refraining from subtyping mammary carcinomas based solely on the evaluation of a TP specimen.

Highly atypical epithelioid cells are not always epithelial (2 cases)

Case 4

A 49-year-old woman presented with an enlarging palpable mass in the right breast. An ultrasound showed the presence of a large fluctuating cyst. An FNA biopsy was performed and the TP slide showed single epithelioid cells with prominent nucleoli and degenerative changes in the absence of a cystic background. The diagnosis rendered was suspicious for adenocarcinoma. A subsequent resection showed benign breast parenchyma with a cyst lined by apocrine metaplastic epithelium, reactive changes, and focal cytological atypia. (Figure 1; G and H)

This case underscores the importance of clinical, radiologic, and pathologic correlation. In retrospect, the clinical presentation of this patient was that of a benign lesion. Although cystic lesions of the breast may present in women of any age, they are most common in those who are between 30 and 50 years of age. They may be associated with nipple discharge or a palpable mass or constitute an incidental finding on screening mammography.¹⁶ Simple cysts usually correspond to BI-RADS 2 and are managed as benign lesions with radiographic follow-up. Complex cysts carry a low risk of malignancy (0.2%) and are managed with aspiration or close follow-up.¹¹ Therefore, when facing an aspiration specimen from a breast cyst, like in the abovementioned case, a malignant diagnosis should be rendered with caution.

The lining of apocrine cysts often sloughs off and can fold onto itself, which may appear as papillary clusters cytologically.¹⁷ These detached fragments tend to aggregate. In a way akin to ductal cells, benign apocrine cells often form cohesive, regular, flat sheets. However, unlike ductal cells, single intact apocrine cells are common.¹¹ Nuclear features are more pronounced in TP, and the prominent nucleoli and cytological atypia of apocrine cells are potential diagnostic pitfalls.^{6,18} Moreover, TP preparations are associated with a decreased size of cell clusters, more fragmented large branching sheets, and a higher number of single cells resulting in apparent dyshesion.⁶ It is important to look for single cells, increased cellularity, and nuclear cytoplasmic ratio in the appropriate clinical context before a diagnosis of malignancy is rendered or suspected based on the evaluation of a TP slide.^{11,13}

Case 5

A 48-year-old woman presented with a palpable right breast mass located at 12 o'clock position, 6 cm from the nipple. Ultrasound revealed a cyst measuring $0.6 \times 0.6 \times 0.5$ cm. An FNA was performed and 30 mL of slightly cloudy colorless fluid was submitted for cytological examination. The TP sample was hypercellular with abundant atypical epithelioid cells with evident nucleoli, concerning for malignancy. The findings on a subsequent excisional biopsy were diagnostic of fat necrosis. (Figure 1; I and J)

Fat necrosis is a benign non-suppurative inflammatory process of adipose tissue. Patients may present with a breast lump, which can mimic malignancy on clinical and mammographic examination.¹⁹ Fat necrosis in the breast is a common pathologic condition with a wide variety of presentations on mammography, ultrasound, and MRI.²⁰

Aqel *et al.* studied 35 cases of fat necrosis diagnosed by FNA.¹⁹ The cytological findings include presence of tissue debris, degenerated fat, and collections of foamy and multinucleated histiocytes.²⁰ The presence of foamy histiocytes in a cytologic sample favors a benign diagnosis, although they can also be present in carcinomas. Nevertheless, the filtration step during TP processing might result in the removal of cellular debris, which is one of the cytologic features of fat necrosis. Furthermore, TP processing might lead to clumping of the epithelioid histiocytes and a more visible and prominent nucleolus, raising the suspicion of malignancy.⁶ In questionable cases, immunohistochemical studies for CD68 and cytokeratin can be of use.²¹

In the current case, the cellularity of the sample along with the cellular atypia was concerning for malignancy. Important criteria for the distinction of malignant from benign breast lesions in cytology preparations are the presence of high cellularity as well as cellular atypia in malignant lesions.²¹² However, exceptions to this rule include fibroadenoma and reactive/degenerative conditions such as fat necrosis, which despite being benign can present as highly cellular specimens with atypia.¹²

Implant associated seroma

Case 6

A 52-year-old woman with a prior history of bilateral silicone breast implants sought medical attention due to left breast swelling 9 years post implant. Ultrasound evaluation revealed a peri-implant multiloculated seroma and an FNA was performed. The TP specimen was highly cellular with dispersed atypical cells with coarse chromatin and numerous mitoses. Occasional cells with kidney-shaped nuclei were observed. Immunohistochemical stains performed on a concurrent cell block preparation showed that the tumor cells were positive for CD3, CD30, and Granzyme B while negative for CD20 and ALK. The diagnosis of breast implant associated anaplastic large cell lymphoma (BIA-ALCL) was rendered. (Figure 2)

Primary breast lymphomas are rare and most of them are of the B cell lineage. BIA-ALCL is a lymphoma of T cell or null phenotype of extremely rare occurrence, with an annual incidence of 0.1 to 0.3 cases per 100,000 women with breast implants.²² The most common

presentation of BIA-ALCL is a peri-implant seroma, followed by a breast mass and seroma.²³

Current recommendations by the Late Periprosthetic Fluid Collection after Breast Implant Working Group are the aspiration and cytological evaluation of any periprosthetic effusion occurring 1 year after implant surgery.²⁴ Cytologic evaluation plays an important role in the diagnosis of BIA-ALCL. Cases in which histological analysis of capsulectomy specimens failed to detect lymphoma after a diagnosis of BIA-ALCL by cytology have been reported.²⁵ Moreover, even though BIA-ALCL can be associated with a grossly normal implant capsule,²⁶ the College of American Pathologists recommends representative sampling of normal appearing capsules,²⁷ underscoring the importance of the cytological evaluation of the seroma fluid. BIA-ALCL is positive for T cell markers such as CD3, CD5, CD30, cytotoxic granule associated proteins such as TIA-1, granzyme B and perforin and negative for B cell markers such as CD20. Importantly, and akin to cutaneous ALCL, BIA-ALCL is usually ALK-negative.²⁸ Flow cytometry has been shown to be a useful diagnostic method in the diagnostic evaluation of effusions or tissue samples.²⁹

Wu *et al.* described findings of flow cytometry studies in two patients with BIA-ALCL. The tumor cells showed strong expression of CD30 and although most lack T-cell antigens, they could express weak CD15, and CD40.²⁹

Other authors confirmed these findings and additionally identified frequent CD4 expression; marked loss of other T cell antigens, including CD3; expression of activation markers; and variable expression of myeloid markers. In isolation, these flow cytometry findings could represent a diagnostic challenge and warrant correlation with morphological and clinical characteristics.³⁰

Surgical excision is the mainstay of treatment and patients who undergo complete excision, which entails implant removal, total capsulectomy and excision of the lesion with negative margins, demonstrate a better survival rate than those managed with limited surgery, chemotherapy or radiation.²³ Patients presenting with a peri-implant effusion have an excellent clinical course, while those presenting with a mass have a worse outcome.³¹

The risk of ALCL in patients with breast implants, albeit low, should raise awareness of this entity in the setting of peri-implant seroma of late occurrence. Furthermore, BIA-ALCL should always be included in the differential diagnosis of patients with prior history of breast carcinoma and similar clinical-radiological presentation.

Conclusions

The TP slide preparation following breast FNA has practical advantages as it eliminates the need for smearing slides and securing proper cellular fixation. This facilitates a more seamless procedure for surgeons or radiologists especially in instances when immediate assessment is not readily available. This technique results in a monolayer of cellular material devoid of obscuring elements with a better cellular preservation and is associated with a low number of non-diagnostic specimens. As with other preparations, there are subtle cytomorphologic findings inherent to this technique that should be taken into consideration:

a) The morphological difference of background bipolar cells that may have preserved cytoplasm render the discrimination of this classic pitfall between fibroadenoma and low grade carcinoma on TP slides even more difficult; b) Solid papillary carcinoma has a single cell, plasmacytoid appearance on TP; c) Nuclear features such as prominent nucleoli are more pronounced in TP so the threshold for cytological atypia should be higher; d) Epithelioid histiocytes, which could be easily recognized on regularly smeared slides, show enhanced cellular and nuclear details on TP material and thus raise the suspicion of carcinoma; and e) The diagnosis of BIA- ALCL should especially be considered in patients with prior history of breast carcinoma. Cytopathologists should exercise caution when interpreting FNAs if TP is the only available diagnostic material. Familiarity with artifacts associated with TP is essential to avoid diagnostic misinterpretations.

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Figure 1.

Figure 2.