Fine Needle Aspiration of Breast Cytology

4

Rana S. Hoda and Rema A. Rao

Breast carcinoma is the most common malignant tumor and the leading cause of carcinoma-related deaths in women worldwide [1]. Fine needle aspiration (FNA) continues to play an integral part in the pre-operative assessment of a breast mass [2, 3] and is the least invasive, fastest, and most cost-effective technique available. Although needle core biopsy (NCB) has largely replaced FNA for diagnosing most solid breast lesions, particularly in the USA, FNA is still used in most countries and displays good clinical performance [1–4].

4.1 FNA and NCB of Breast

The NCB has a better sensitivity than FNA (87% versus 74%) with similar specificity (98% versus 96%) [1, 4]. The indications for FNA include confirmation of the targeted nodule prior to performing NCB, sampling of cystic breast lesions, lesions difficult to access via NCB, and for diagnosis of metastatic disease [1–3]. The diagnostic sensitivity of FNA ranges from 74% to 99%, specificity ranges from 60% to 100%, and accuracy from 72% to 95%. The false-negative and false-positive rates of FNA ranges from 1.7% to 13.3% and from 0.6% to 6.5% respectively [2, 3].

R. S. Hoda, MD (✉)
CBLPath, Rye Brook, NY, USA
e-mail: rhoda@cblpath.com

R. A. Rao, MD
Papanicolaou Cytology Laboratory, Weill Cornell Medicine/New York Presbyterian Hospital, New York, NY, USA
e-mail: rer9052@med.cornell.edu

4.2 Advantages and Limitations of FNA of Breast

The "triple test" approach is utilized to accurately analyze a breast mass. The triple test uses the clinical and radiological findings, and cytological features on breast FNA to arrive at a diagnostic interpretation. If all three findings are positive, the diagnostic accuracy for a malignant neoplasm approaches 100% [5].

The advantages of FNA of breast lesions include: (1) the ability to sample cystic lesions; (2) the ability to sample lesions that are difficult to access through NCB, such as lesions in the retroareolar location and chest wall recurrence of breast carcinoma; (3) detecting metastatic breast carcinoma in bone, lungs, and body cavity fluids; and (4) ability to perform prognostic and predictive markers on FNA material from metastatic sites.

Limitations of breast FNA include: (1) Inability to distinguish *in situ* ductal carcinoma (DCIS) from invasive carcinoma of no special type (NST); (2) inability to distinguish low-grade ductal carcinoma from fibroadenoma and atypical epithelial hyperplasia; and (3) inability to perform prognostic and predictive markers, such as Her2-neu in primary breast carcinoma [2, 3, 5].

4.3 Slide Preparation and Staining Techniques

Conventional smears and cellblocks have traditionally been used as the preferred preparations from an FNA of the breast. However, liquid-based preparations (LBP), including ThinPrep (TP; Hologic, Boxborough, MA) and SurePath (SP; BD Diagnostics, Burlington, NC), are increasingly being used as either sole preparations or in conjunction with the traditional preparations for diagnosing breast lesions. Although the LBP produce minor changes in cytomorphology and background features, the diagnostic sensitivity and specificity are similar to conventional preparatory techniques [6].

S. Stolnicu, I. Alvarado-Cabrero (eds.), *Practical Atlas of Breast Pathology*, https://doi.org/10.1007/978-3-319-93257-6_4

Slide preparations include conventional smears (CS), cytospins, LBP (including TP and SP), and cellblocks (CB). The CS and cytospins can be air-dried and stained with Romanowsky stain or alcohol-fixed and stained with Papanicolaou (Pap) stain. LBP are alcohol-fixed and stained with Pap stain. Hematoxylin and eosin (H&E) stain is used to stain CB sections [2, 6].

The CS can also be stained with ultra-fast (UF) Pap stain. This is a modified Pap stain that hemolyzes the background blood and makes cells flatter and larger due to air-drying and rehydration in saline. In addition, the alcohol fixative used in this process contains formalin. This stain can be performed in 90 seconds and is thus termed ultra-fast. UF-Pap stain has similar background, nuclear staining, and cell morphology as the standard Pap stain [7].

Multiple studies have demonstrated the utility of LBP for breast FNA. Aside from some minor cytomorphological and background differences between LBP and CS, LBP has been shown to be a reliable technique with a diagnostic accuracy equivalent to CS. The advantages include a single standardized and uniform preparation with no obscuring elements, which makes it easier to screen and interpret. Ancillary tests, such as immunocytochemistry, can be formed on additional LBP. Collection technique is uniform and the sample collection vial, containing preservative solution, is easier to transport and store. The main disadvantage of LBP is that on-site adequacy assessment cannot be performed.

Cytological alterations in LBP include: (1) Cells appear smaller; (2) cell groups may become fragmented, and more single cells may be seen; (3) epithelial cells may become dissociated with stromal components, such as in fibroadenoma; (4) due to immediate liquid fixation, nucleoli may become apparent even in benign lesions; and (5) myoepithelial cells may retain their cytoplasm and mimic cells of invasive ductal carcinoma. The main alteration in the background features include reduced or lack of background elements such as mucin or necrosis, and the background material tends to clump instead of being diffuse as seen in CS [6].

4.4 Reporting of Breast FNA

In 1996, the National Cancer Institute (NCI) in the United States proposed the probabilistic approach of breast FNA, based on cytological features, for uniform reporting. The NCI approach has been widely adopted and is comprised of five diagnostic categories: unsatisfactory (C1), benign (C2), atypical (C3), suspicious/favor malignancy (C4), and malignant (C5). The International Academy of Cytology is developing a reporting system similar to the NCI version. A draft of the system will soon be available at the IAC website for review and critique by breast pathologists [8, 9].

4.5 Benign Epithelial Cells

The morphology of ductal and lobular epithelial cells varies with the age of the woman, phase of menstrual cycle, and pregnancy. The majority of ductal epithelial cells are columnar or cuboidal. The cytoplasm contains abundant organelles involved in secretion. Histologically, myoepithelial cells lie between the epithelial cells and basal lamina. Cytologically, they are dark and crescentic, are interspersed between ductal epithelial cells, and appear in different planes of focus. The lobules, both histologically and cytologically, appear as rounded clusters comprising round-to-cuboidal cells with vacuolated cytoplasm (Fig. 4.1) [1–3].

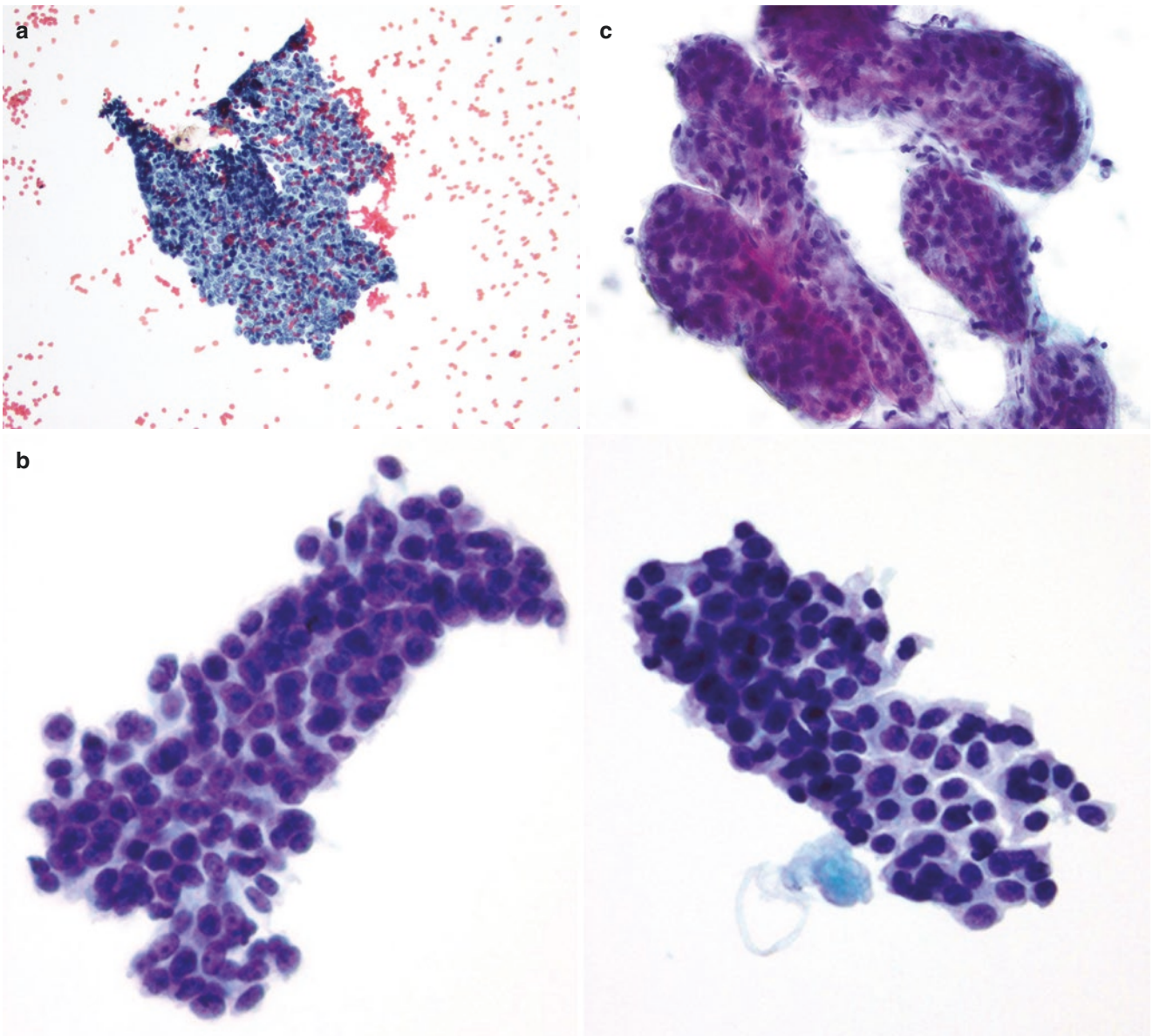


Fig. 4.1 Benign ductal and lobular cells: (**a**) Benign ductal cells in a conventional smear show cohesive sheets and tight clusters of cells with bland nuclei, pale nuclear chromatin, and small inconspicuous nucleoli. Myoepithelial cells appear as darker crescentic cells on a different plane of focus than epithelial cells (Pap stain); (**b**) Benign ductal cells in a ThinPrep shows ductal cell groups with regular thin nuclear membranes, pale chromatin, and small inconspicuous nucleoli. Note the darker myoepithelial cells. Cytological features are similar to those seen in the CS. However, the background is clean (Pap stain); (**c**) Benign lobules are composed of terminal ducts and many small acini. Flattened myoepithelial cells surround the tight cohesive group of benign terminal ductal epithelium (TP, Pap)

4.6 Non-neoplastic Entities

4.6.1 Cystic Apocrine Metaplasia

Apocrine metaplasia can occur in any benign proliferative lesion. Histologically, cystic apocrine metaplasia is composed of flat cuboidal cells, which may form a single layer or as blunt papillae. The cells are evenly spaced with round nuclei with nucleoli and abundant finely granular eosinophilic cytoplasm (Fig. 4.2) [1–3, 6].

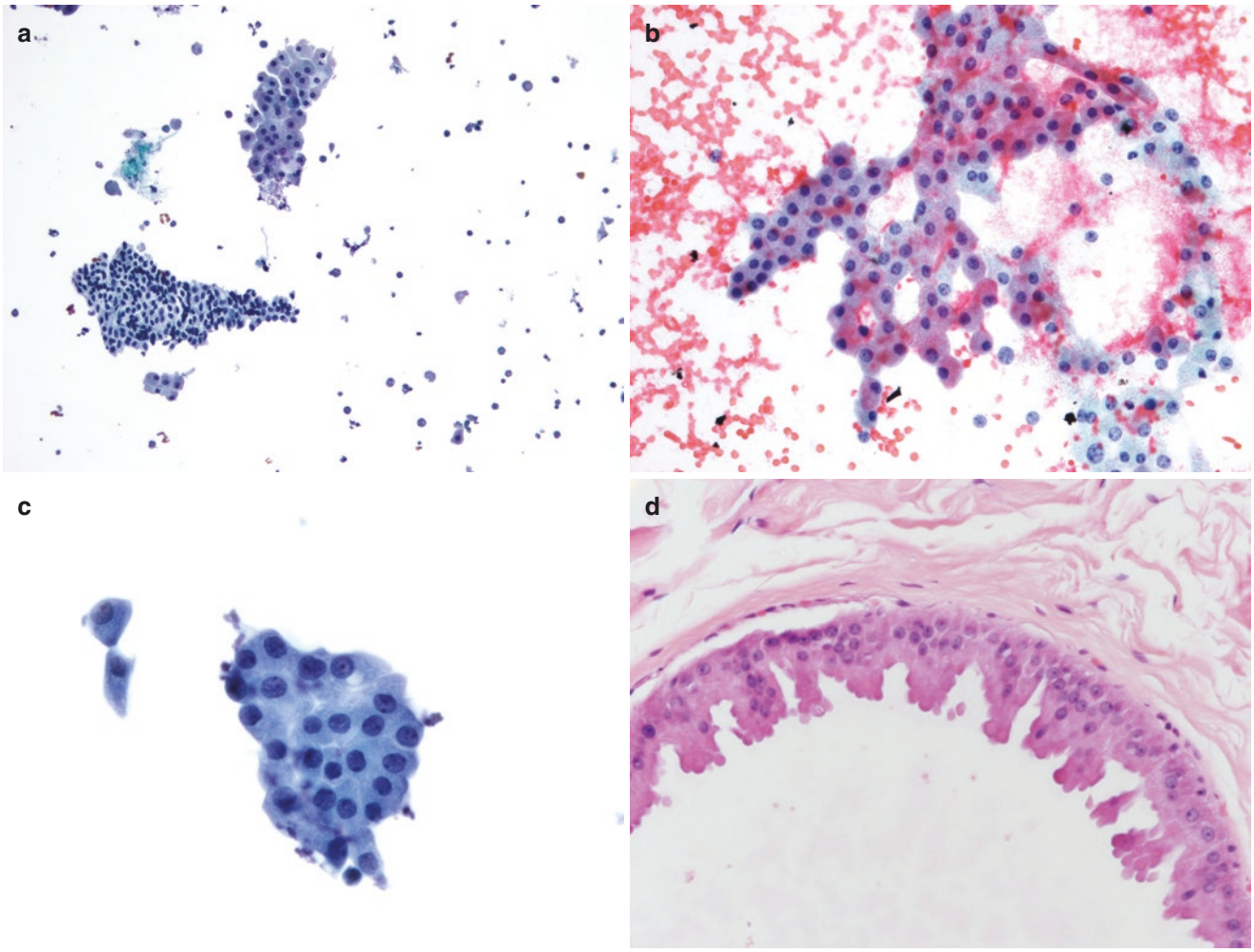


Fig. 4.2 Fibrocystic change with apocrine metaplasia: (**a**) A benign ductal cell group with no cytologic atypia, noted adjacent to a group of apocrine metaplastic cells. The apocrine metaplastic cells contain abundant granular cytoplasm, well-defined cellular outlines, round nuclei, prominent nucleoli, and bland chromatin. The background elements of foamy histiocytes and cystic debris are retained (TP, Pap); (b) Apocrine metaplastic cells in conventional smear: The cells have moderately abundant granular cytoplasm, well-defined cellular outlines, round and regular nuclei, small nucleoli and bland chromatin. Note abundant background blood (Pap stain); (**c**) Apocrine metaplastic cells in ThinPrep: Higher magnification of the apocrine metaplastic cells showing similar features as the conventional smear. Lack of blood in the background allows for better appreciation of cytology (Pap stain); (**d**) Apocrine metaplastic cells in histology: Excisional biopsy shows a cystically enlarged duct lined by apocrine cells, a feature of non-proliferative fibrocystic change or apocrine cyst (H&E)

4.6.2 Fibroadenoma

Fibroadenomas comprise one-fifth of all benign breast masses and usually occur at a mean age of 30 years. It clinically presents as a palpable, painless, firm, and solitary mass. The non-palpable fibroadenoma are detected on imaging. Fibroadenomas arise from the epithelium and stroma of terminal duct-lobular units. Histologically, epithelial and stromal components are noted. Squamous and apocrine metaplasia and duct hyperplasia may be seen within the epithelial component. Fibroadenomas are frequently sampled and diagnosed by FNA. Accurate cytological diagnosis of this common benign lesion is important so that the patient can be treated by conservative surgery or clinically followed. Cytological findings should be correlated with clinical and imaging findings. Cytologically, a confident diagnosis of fibroadenoma shows staghorn epithelial configurations, stromal fragments, and numerous background myoepithelial cells, some of which appear as stripped nuclei (Fig. 4.3). However, fibroadenoma is a well-recognized source of false-positive diagnosis and may be misdiagnosed as a low-grade ductal carcinoma because of shared cytomorphologic features [1–3, 6, 10].

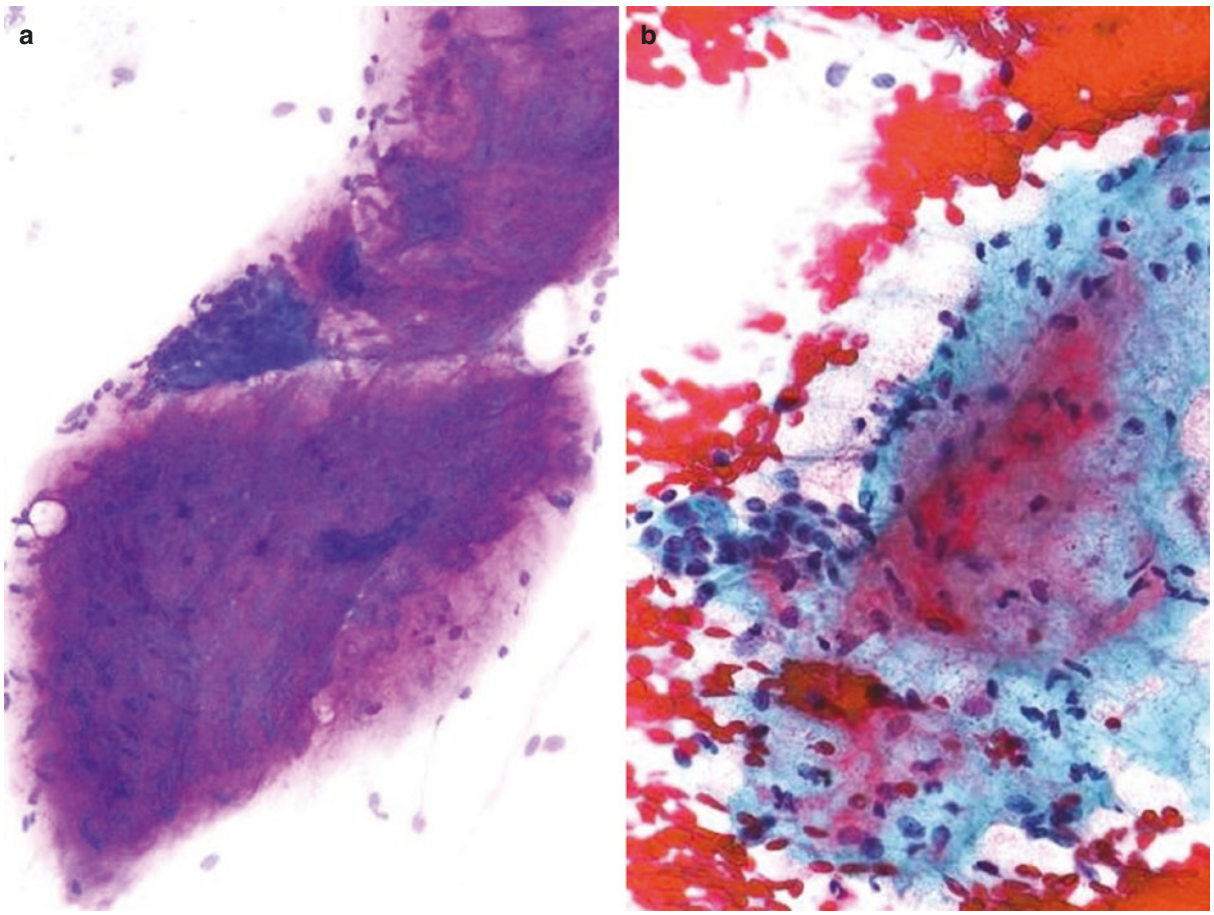


Fig. 4.3 Fibroadenoma: (**a**, **b**) FNA of fibroadenoma are characterized by staghorn arrangements of epithelial cells intermixed with spindled cells embedded in stromal fragments. The nuclei can occasionally show atypia that can be mistaken for malignancy. In these CS, the stromal fragments are intermixed with benign ductal cell groups. The stromal fragments stain magenta on air-dried Romanowsky stain (DQ stain) (left) and greenish-blue on alcohol fixed Pap stain (right); (**c**, **d**) ThinPrep shows clusters of tightly cohesive ductal cells with minimal nuclear atypia and stromal fragments. The background is clean with singly-distributed myoepithelial cells with oval-to-crescentic dark nuclei and scant cytoplasm. In CS, these cells appear as "stripped nuclei." The diagnosis of fibroadenoma may be more difficult on LBP, due to epithelial cells and stromal dissociation. Moreover, in LBP, the myoepithelial cells may retain their cytoplasm and may mimic isolated cells of IDC (TP, Pap); (**e**) Excisional biopsy of fibroadenoma showing the biphasic morphology with elongate staghorn-like benign ductal elements and a background bland appearing hypocellular stromal component with no nuclear atypia, mitoses, or necrosis (H&E)

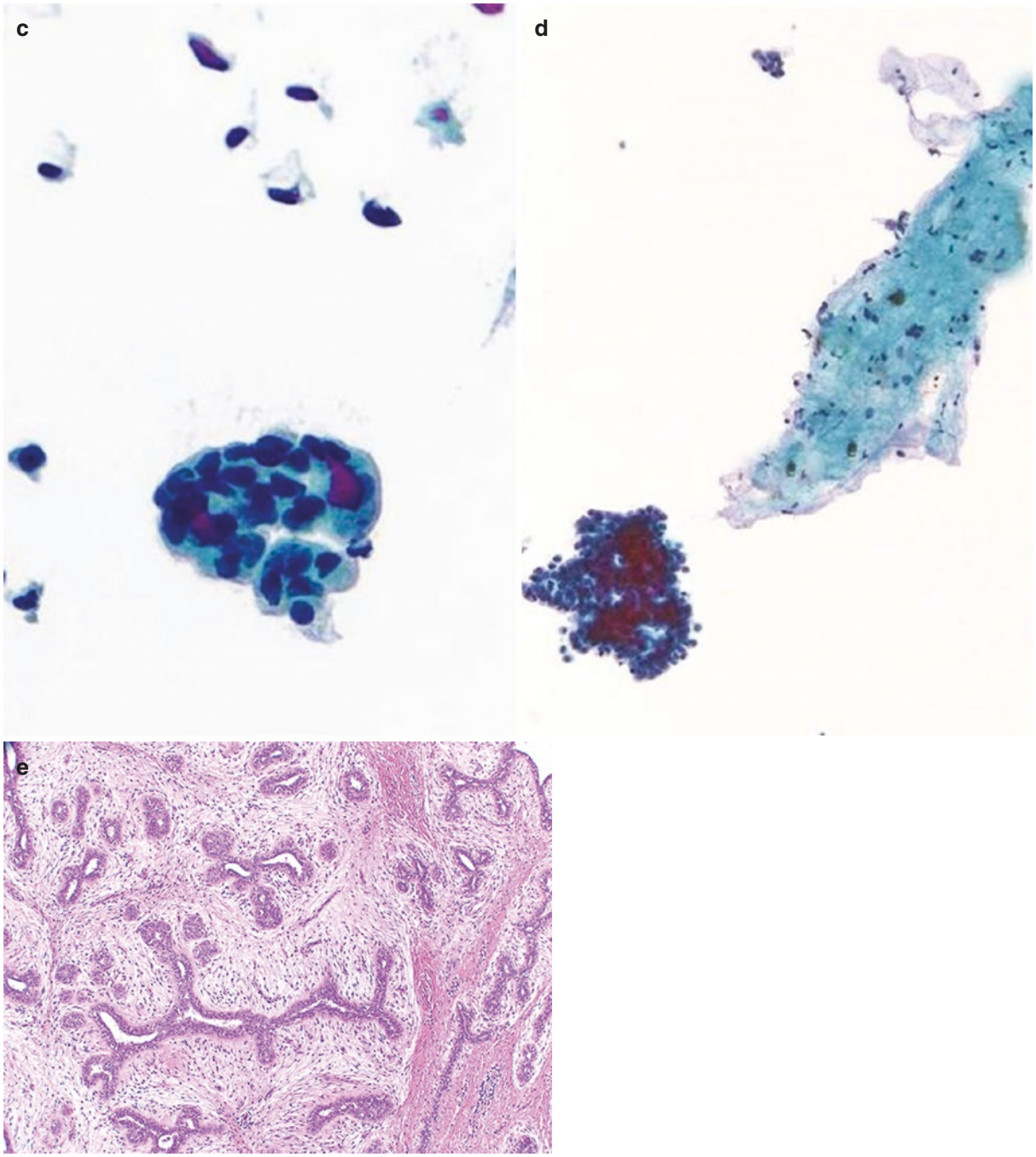


Fig. 4.3 (continued)

4.6.3 Lactational Change

In pregnancy, secretory changes occur evenly throughout the breast. The terminal ducts and the lobules enlarge, with the latter being of different shapes and irregularly distended. Histologically, the cells within the lobules enlarge and proliferate and display vacuolated cytoplasm, hyperchromatic nuclei, and prominent nucleoli. Cytologically, the architectural and cellular features are similar to histology and are also similar in CS and LBP. In addition, the background shows lipid droplets and proteinaceous material with "stripped" nuclei with prominent nucleoli embedded within. FNA of breast masses in pregnant or lactating women is an uncommon procedure, and cytological interpretation is considered problematic due to atypia inherent to secretory change in glandular epithelia (Fig. 4.4) [6, 11].

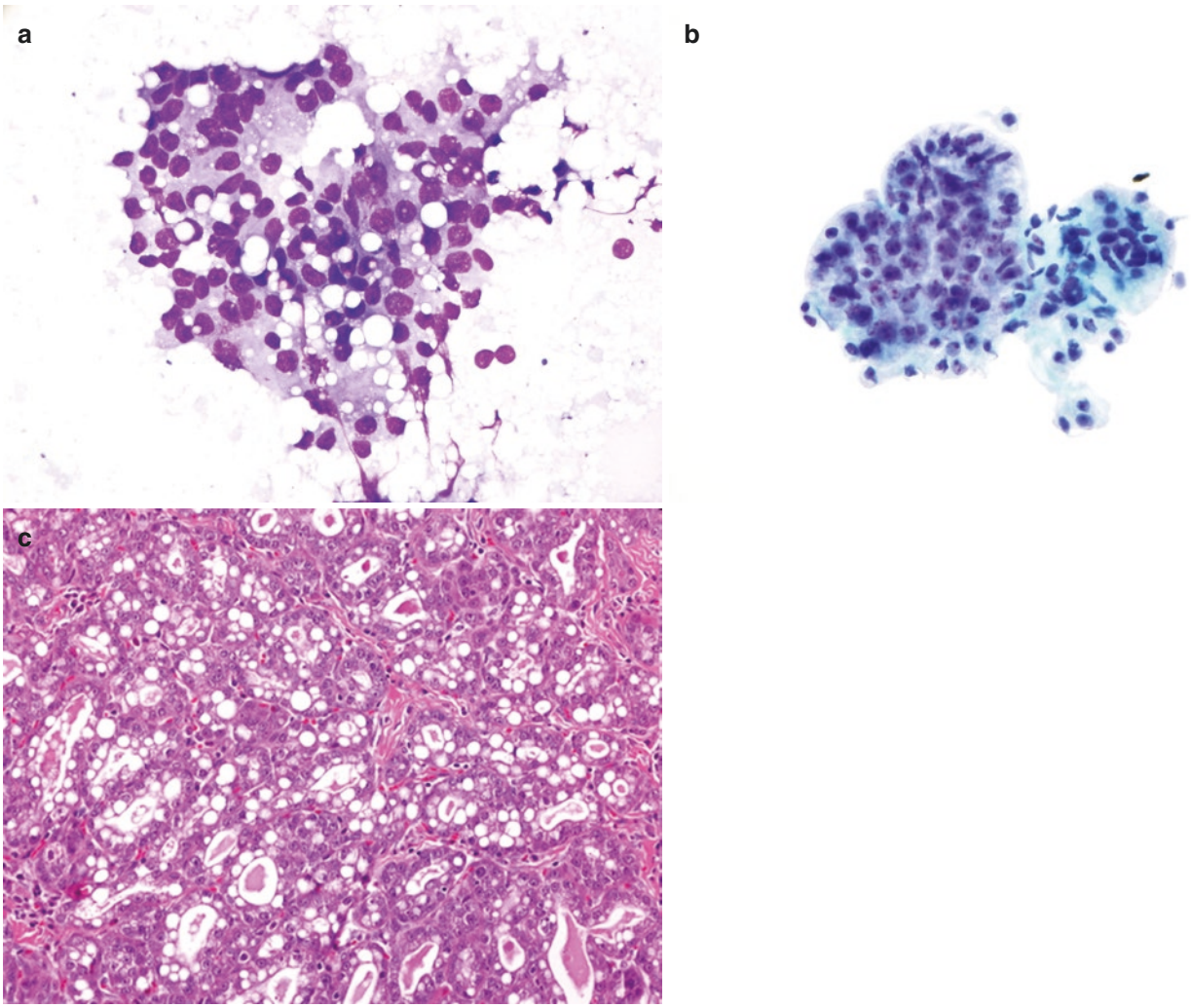


Fig. 4.4 Lactational adenoma/change: (**a**) Lactational adenoma/change presents as a well-circumscribed mass during or immediately after pregnancy. FNA specimens tend to be hypercellular. In this conventional smear, the ductal cell groups are loosely cohesive and show nuclear enlargement without size variation, foamy cytoplasm, and prominent nucleoli. "Bare" nuclei are present in the background. Conventional air-dried smears tend to best show the foamy material in the background, whereas the LBP tend to have a clean background (DQ stain); (**b**) In ThinPrep, the ductal cells are arranged as cohesive groups, appear monotonous, with prominent nucleoli; the cytoplasm is foamy and delicate. All background elements of lactational adenoma/change are retained in LBP, but may be reduced and tend to be more cohesive rather than being diffuse (Pap stain); (**c**) Excisional biopsy of lactational adenoma/change: shows hypersecretory change in mammary glands with closely packed glands and abundant luminal secretions. The lesional cells are similar to those on cytology (H&E)

4.6.4 Fat Necrosis

Fat necrosis may result from trauma, prior surgery, or radiation therapy, and may affect any part of the breast. Patients usually present with a superficially located painless breast mass with retraction of the overlying skin. Fat necrosis may be difficult to distinguish from breast carcinoma, both clinically and radiologically. Histologically, fat necrosis initially shows disruption of fat and hemorrhage, followed by infiltration of histiocytes, some containing hemosiderin, foreign-body giant cells, other inflammatory cells, and occasional foci of calcifications. Fibrosis occurs in late stages. Cytological features are similar to histological features (Fig. 4.5) [1–3, 6].

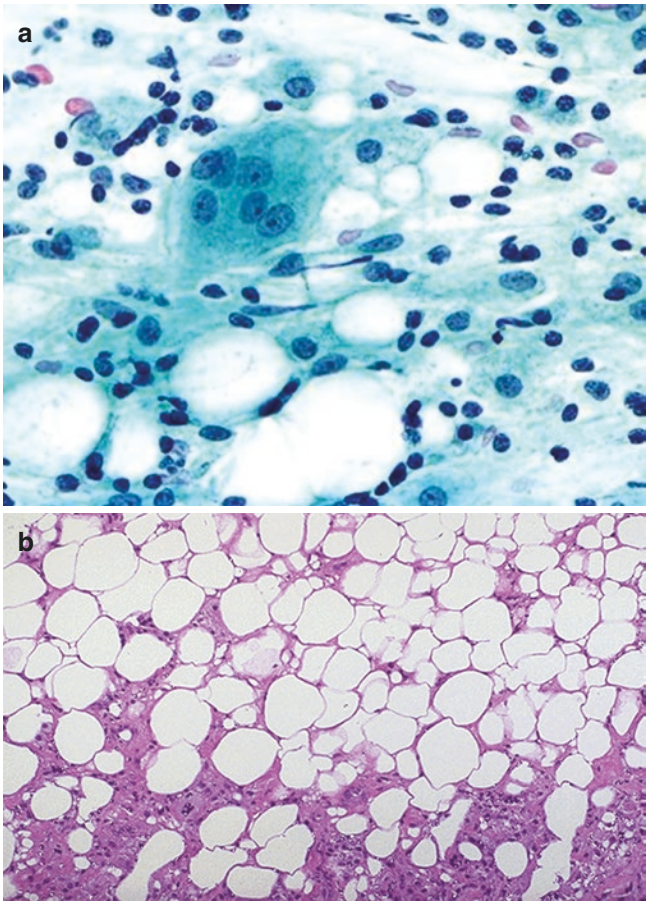


Fig. 4.5 Fat necrosis: (**a**) Aspirates of fat necrosis are usually hypocellular and consist predominantly of histiocytes some forming multinucleate and pigmented giant cells, with coarse vacuolated cytoplasm, on a background of fibroadipose tissue. Occasional foci of calcification may also be seen (CS, Pap); (**b**) Fat necrosis on the corresponding biopsy shows necrotic adipocytes and intermixed histiocytes that are similar to those on cytology (H&E)

4.7 Atypical Breast Lesions

Histologically, ductal hyperplasia without atypia shows orderly epithelial growth with varied structural patterns. The nuclei are smooth, round, oval-to-spindly and may show uneven spacing and overlap. Nucleoli are not conspicuous, chromatin distribution is uniform, cytoplasm is scant and may appear vacuolated. Nuclear-to-cytoplasmic (N:C) ratio is low [1]. In contrast, atypical ductal hyperplasia (ADH) is a proliferative lesion, which fulfills some, but not all criteria for DCIS. ADH may show a solid, cribriform, micropapillary or papillary growth patterns. The nuclei are enlarged, hyperchromatic, with irregular chromatin distribution and nucleoli. N:C ratio is high. Mitoses may be seen [1].

Cytologically, atypical diagnosis poses a management dilemma. The NCI atypical category C3 is characterized by cytological features between clearly malignant or clearly benign, thus making a definitive cytological diagnosis impossible [12]. The rate of C3 is 3–7% of all breast FNA. Causes of atypical diagnoses include sampling and technical reasons such as low cellularity and smear-related artifacts of air-drying, thick cellular areas, and excess blood. Cytopathologists' experience may lead to misinterpretation, such as overcall of atypia that is occasionally seen in a fibroadenoma as atypical. Unfamiliarity with cytomorphologic features on LBP may also cause misinterpretation (Fig. 4.6) [1–3, 6, 12].

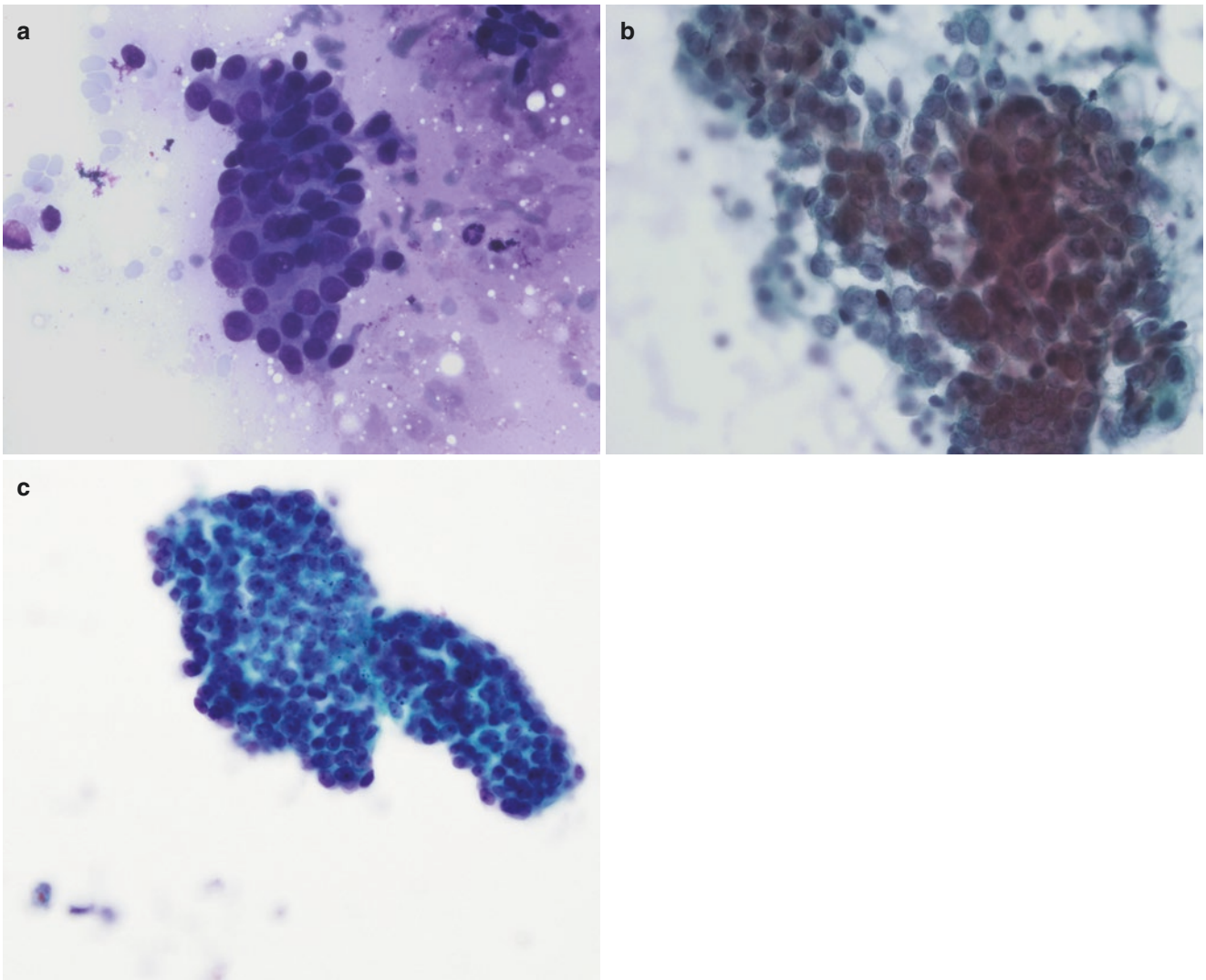


Fig. 4.6 Atypical: (**a**) A loosely cohesive cluster of ductal cells with nuclear enlargement, loss of polarity, and high N:C ratio. Note the single cells with similar cytology in the background. Scant cellularity of these atypical ductal groups precludes a more definitive interpretation and therefore this aspirate is best classified as "atypical" (CS, DQ); (**b**) A cohesive cluster of ductal epithelial cells with nuclear enlargement, overlap, loss of polarity, high N:C ratio, and prominent nucleoli. Scattered in between these atypical ductal cells are dark and crescentic myoepithelial cells. The overall findings raise the possibility of sampling of DCIS or atypical ductal hyperplasia, although these entities are not definitively diagnosed on cytology and therefore best classified as "atypical" (CS, UFPAP); (**c**) A single tight cohesive cluster of ductal cells reminiscent of a "staghorn" cluster in a fibroadenoma, Fibroadenoma (FA) but exhibit cytologic atypia with nuclear enlargement, overlap, and prominent nucleoli, and therefore best classified as "atypical." Note similarity with the conventional smears (TP, Pap)

4.8 Neoplastic Entities

4.8.1 Breast Cancer

Breast carcinoma is the most common malignant tumor in women and the leading cause of carcinoma-related deaths in women worldwide. Breast cancer makes up 25% of all new cancer diagnoses in women globally [1]. Breast carcinoma can be of no special type or lobular type and can be in situ or invasive. Cytology cannot distinguish between in situ or invasive disease due to similar cytomorphology of malignant cells and lack of cytological criteria that can accurately identify invasive carcinoma. This chapter will therefore describe only invasive breast carcinoma.

4.8.2 Invasive Carcinoma of No Special Type (NST)

Invasive carcinoma of no special type (NST), also previously known as invasive ductal carcinoma, not otherwise specified (NOS), is the largest group of malignant tumors in the breast and accounts for 75–80% of all breast carcinomas. Clinical presentation is usually of a solid mass involving any part of the breast, and it can occur at any age. The initial diagnosis can be made on FNA and NCB. Histologically, the tumors can be graded into well, moderately, and poorly-differentiated, based on architectural and nuclear features and mitotic rate. The advantage of FNA in examining NST is that it can be used as an adjunctive diagnostic test to accurately assess the targeted lesion prior to NCB. The limitations of FNA in examining NST include: (1) false-negative diagnoses due to sampling of tumors with abundant fibrosis where malignant cells may not be adequately aspirated; (2) interpretive issues, where well-differentiated carcinoma of NST type may be misinterpreted as fibroadenoma; (3) false-positive diagnosis may be rendered in fibroadenoma and lactational changes, due to cellular atypia of isolated cells; and (4) inability to grade NST because the parameters used in histologic grading cannot be accurately reproduced in cytology (Figs. 4.7 and 4.8) [1–3, 6].

Although FNA is a reliable method for the diagnosis of breast carcinoma, difficulties in the recognition of the various subtypes of NST still exist [1–3, 6, 13]. Haji et al. [13] concluded that NST, as well as other types of infiltrating breast carcinoma such as mucinous, medullary, apocrine, and papillary, have specific cytomorphological features that differentiate them from one another and from IDC, NST (Fig. 4.8). They described the frequency of 20 cytomorphological features, including architectural pattern, forms of neoplastic cells and their nuclear and cytoplasmic characteristics, accompanying cells, and background materials and semi-quantitative analysis of five features including cellularity, pleomorphism, nuclear irregularity, presence of cells in loose cohesive clusters, and singly dispersed cells. Specific features are discussed in the sections on the four variants of infiltrating breast carcinoma described below.

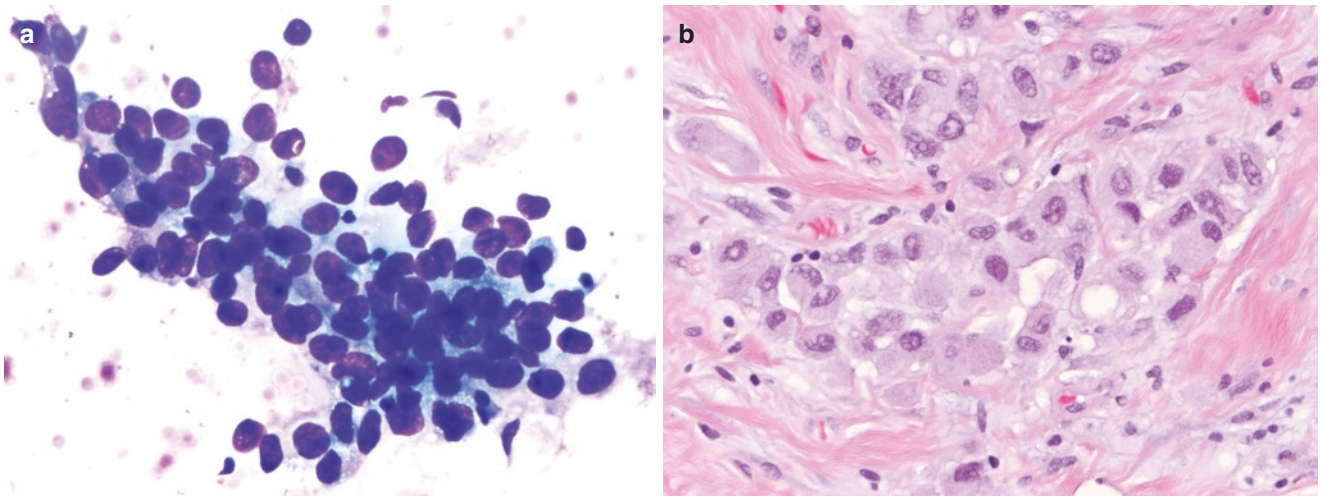


Fig. 4.7 Invasive ductal carcinoma-NST, high-grade: (**a**) The cytomorphologic features are similar to adenocarcinoma seen elsewhere: clusters of three-dimensional (3-D) cells with nuclear pleomorphism, hyperchromasia, and irregular nuclear borders. In this case, the cell clusters are loosely cohesive with nuclear pleomorphism and prominent nucleoli. The cytoplasm is vacuolated. It is not possible to distinguish infiltrating ductal carcinoma (IDC) from ductal carcinoma in situ on cytology alone (CS, DQ); (**b**) Invasive carcinoma-NST, high-grade, on the corresponding histologic section, showing irregular angulated glands composed of cells with similar cytology as previously described (H&E)

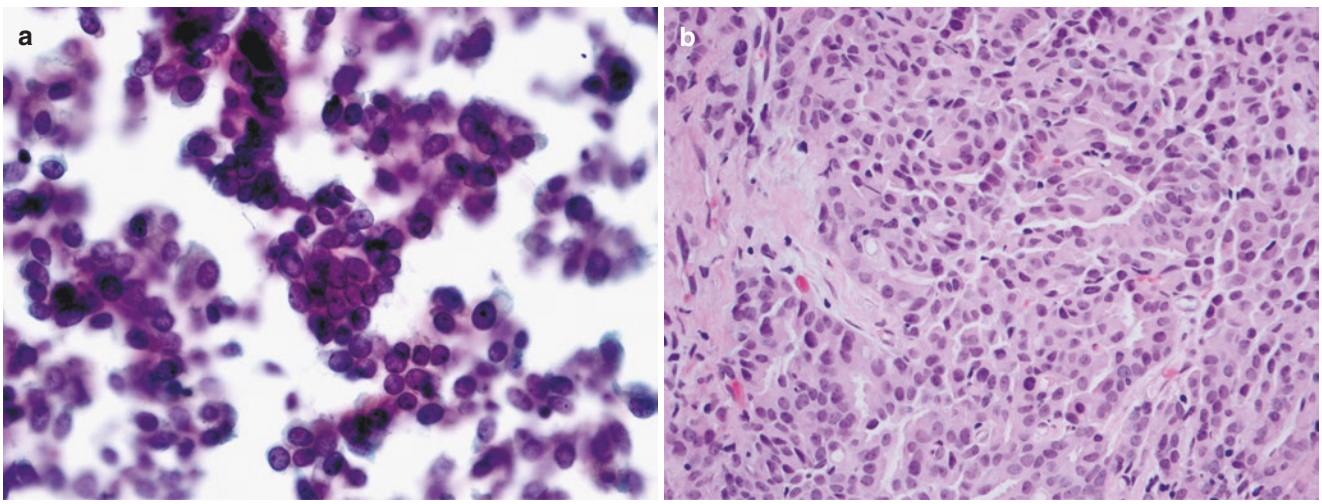


Fig. 4.8 Invasive carcinoma-NST, low-grade: (**a**) Cohesive clusters of malignant cells with low nuclear grade features such as mild-to-moderate nuclear enlargement, mild increase in N:C ratios, fairly regular nuclear membranes and moderately abundant vacuolated cytoplasm seen on Ultra-fast Pap stain (CS, UF Pap); (**b**) Invasive carcinoma-NST, low-grade on concurrent histologic section, showing tumor cells with similar cytomorphology with low nuclear grade and tubule formation (H&E)

4.8.2.1 Tubular Carcinoma

Tubular carcinoma is a highly differentiated infiltrating breast carcinoma accounting for <2% of all female breast carcinomas. Histologically, it is composed of well-defined tubules lined by a single layer of tumor cells and surrounded by abundant fibrous stroma. The tubules are angulated, open, and haphazardly infiltrate the breast parenchyma. The cells are cuboidal or columnar with basally-located round or oval hyperchromatic nuclei, finely granular chromatin, and inconspicuous nucleoli. Cytoplasm is usually amphophilic and apocrine snouts may be seen towards the luminal cell surface. Cytological features are similar to those described for NCB. Most cases of tubular carcinoma are detected by mammography. The sensitivity for the diagnosis of tubular carcinoma is higher with NCB than with FNA. Because of limited sampling, most tubular carcinomas are interpreted as atypical and not outright malignant by FNA. Other histologic types of breast carcinoma may often occur with tubular carcinoma (Fig. 4.9) [1–3, 6].

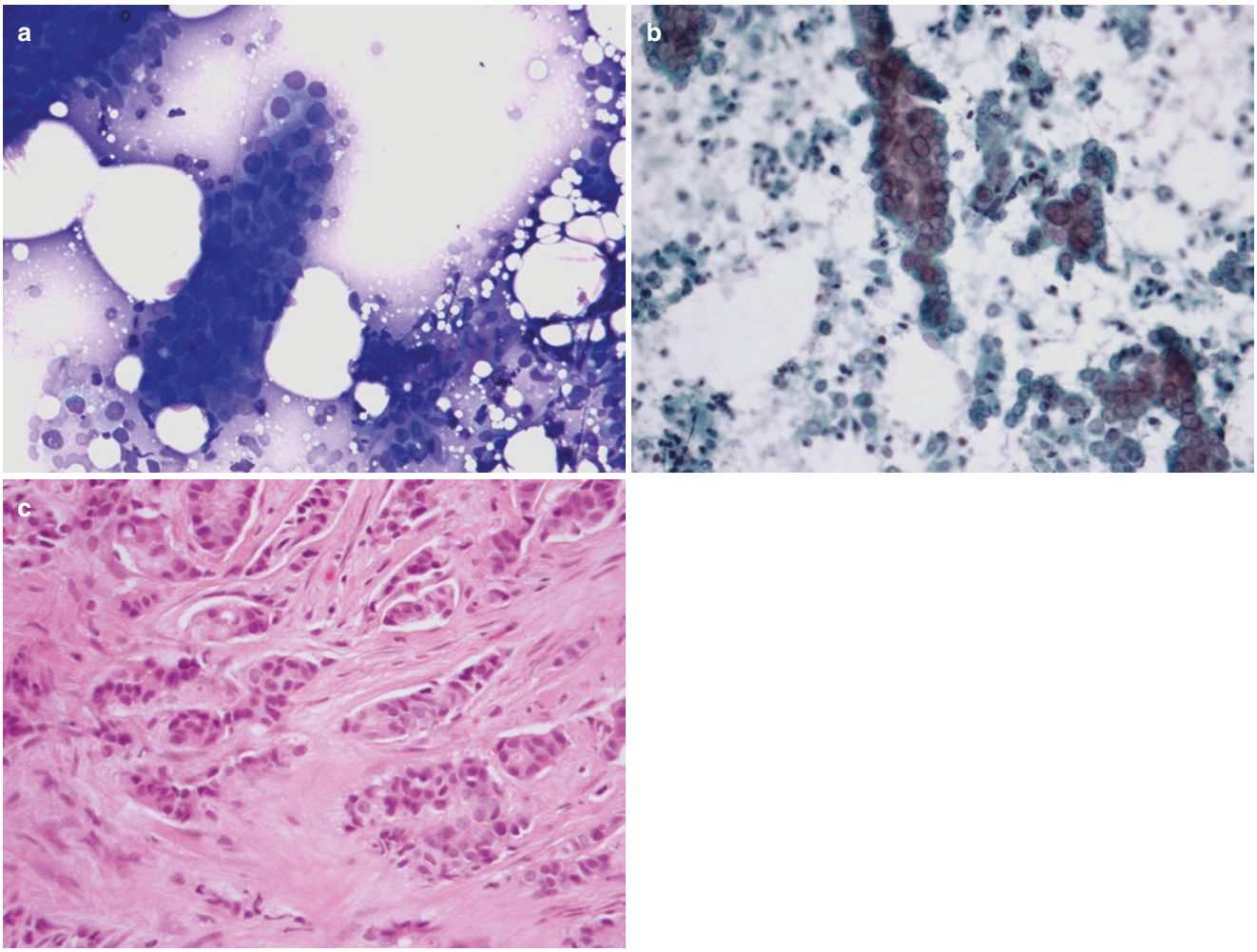


Fig. 4.9 Tubular carcinoma: (**a**) Cohesive clusters of tumor cells in honeycombed sheets and clusters showing tubule formation and low nuclear grade (CS, DQ); (**b**) Cellular aspirate with cohesive clusters of tumor cells with low nuclear grade and prominent tubule like formation (CS, UF Pap); (**c**) Concurrent core biopsy showing the prominent tubule formation and tumor cells with low nuclear grade (H&E)

4.8.2.2 Mucinous (Colloid) Carcinoma

Pure mucinous carcinoma is an uncommon variant of infiltrating breast carcinoma with distinctive histologic and cytologic features, which include loosely cohesive aggregates and acini of bland tumor cells with smooth borders, floating in abundant extracellular mucin. The nuclei may occasionally show moderate pleomorphism. Intracytoplasmic mucin can appear as a large vacuole forming signet-ring cells. Pure or nearly pure mucinous carcinoma diagnosis is restricted to tumors composed of more than (>) 90% of the components described above. Mucinous carcinoma accounts for 2% of all infiltrating breast carcinomas and the usual clinical presentation is of a breast mass. The sensitivity for the diagnosis of pure mucinous carcinoma is significantly higher with NCB than with FNA. Due to limited sampling, cytology cannot distinguish pure mucinous carcinoma from NST type with mucinous features, and should therefore be reported as the latter. Differential diagnosis also includes mucocele of the breast and metastasis of mucinous carcinoma from other sites such as colon, lung, and gynecological tract. In cytology preparations, mucin stains as red-violet to magenta on air-dried Romanowsky-type stains, such as Diff-Quik (DQ) stain and bluish-green on alcohol-fixed Pap-stained slides. Mucinous carcinoma is better diagnosed on DQ-stained CS compared to Pap-stained CS and TP slides (Fig. 4.10) [1–3, 6, 14].

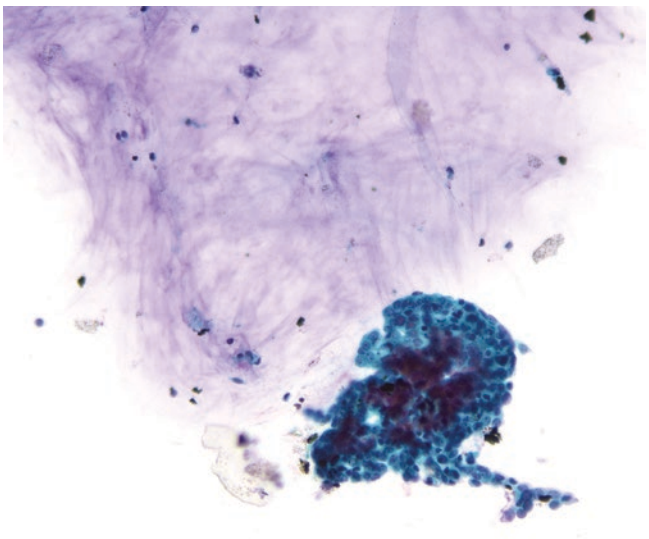


Fig. 4.10 Mucinous carcinoma: the carcinoma cells are present in clusters that float amid abundant extracellular mucin. The malignant cells show moderate to high nuclear grade with vesicular chromatin and prominent nucleoli. Note the rigid borders of both, the dense mucin and the cell cluster. Mucinous carcinoma is better diagnosed on DQ-stained CS compared to Pap-stained CS and TP slides (TP, Pap)

4.8.2.3 Micropapillary Carcinoma

Invasive micropapillary carcinoma is a distinct type of infiltrating breast carcinoma in which the tumor cells are arranged in morule-like clusters. In pure micropapillary carcinoma, at least 75% of the tumor should have this growth pattern. In mixed micropapillary carcinoma, conventional NST type may be the predominant pattern. Due to limited sampling, cytology cannot distinguish the two patterns of micropapillary carcinoma, pure and mixed. Histologically, the carcinoma cells are cuboidal-to-columnar, with granular or dense eosinophilic cytoplasm, with intermediate-to-high-grade nuclei. The clusters of tumor cells have a serrated border and may show a central lumen. Each tumor cell cluster is surrounded by a clear space with intervening stroma. Cytological features are similar to those described on histology. In cytology, this clear space surrounding malignant cell clusters is known as a "lacunar space." Lacunar spaces are commonly seen in almost all malignancies, in the cell block section, CS and LBP (Fig. 4.11) [1–3, 6].

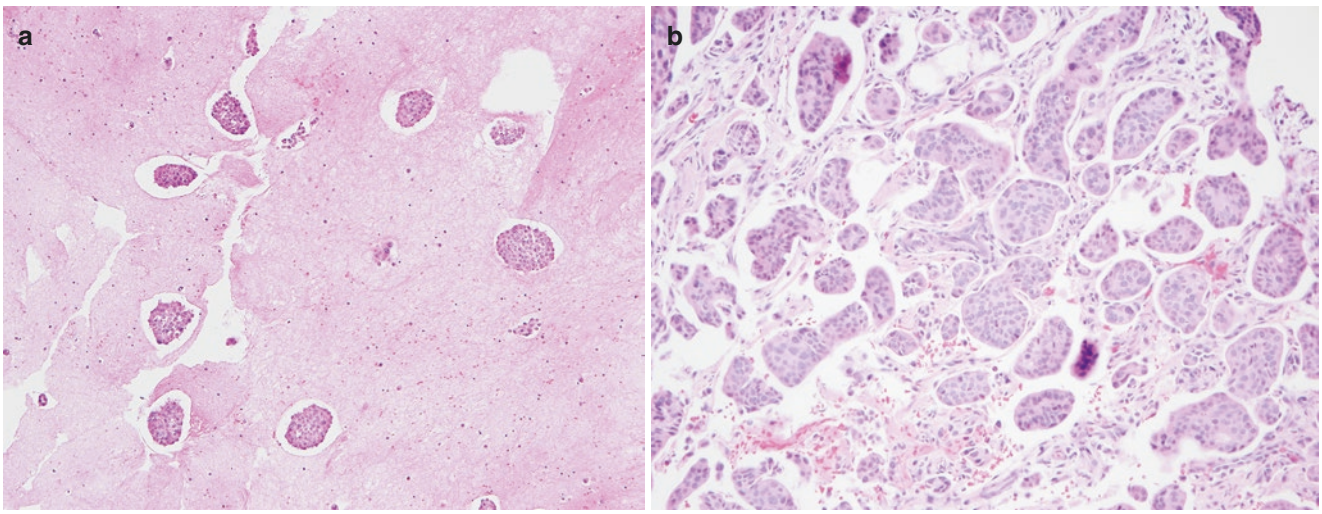


Fig. 4.11 IDC, micropapillary pattern: (**a**) This H&E-stained section of the cell block (CB) made from FNA is characterized by cohesive tufts of cells with nuclear monotony arranged in pseudopapillary structures and surrounded by empty, clear spaces (lacunar space) (H&E); (**b**) H&E-stained sections of the corresponding excisional biopsy showing the tumor composed of morula-like clusters floating in empty, clear spaces lined by delicate strands of stroma. The clusters often have a serrated outer border. They display an inside-out arrangement, with the luminal aspect of the cell present on the outer surface of the cluster (H&E)

4.8.2.4 Apocrine Carcinoma

Apocrine carcinoma is a sub-type of breast carcinoma composed predominantly of malignant apocrine-type cells. It accounts for 1% of all infiltrating breast carcinomas, and the clinical presentation varies from asymptomatic to the presence of a hard, unilateral breast lump with irregular borders. The cells of apocrine carcinoma are reminiscent of apocrine metaplasia and some of these carcinomas probably arise from pre-existing apocrine change. Histologically, the pattern of growth can be similar to NST, although apocrine carcinoma is usually poorly differentiated with more dyscohesion. The tumor cells have abundant eosinophilic, foamy, or granular cytoplasm and large, round, and vesicular nuclei with prominent nucleoli. Nuclear pleomorphism, hyperchromasia, and size of nucleoli vary with the grade of the tumor. Intracytoplasmic lumens with secretions can be seen. Cytology aspirates tend to be moderate to highly cellular with nuclear pleomorphism, overlap, and crowding, irregularity of membranes, macronucleoli, and high N:C ratio. Other cytologic features are similar to those described for histology. Cytological differential diagnoses include apocrine cyst, apocrine metaplasia and apocrine adenosis. Apocrine carcinoma is distinguished from these benign apocrine lesions by the pleomorphic nuclear features (Fig. 4.12) [1–3, 6, 13].

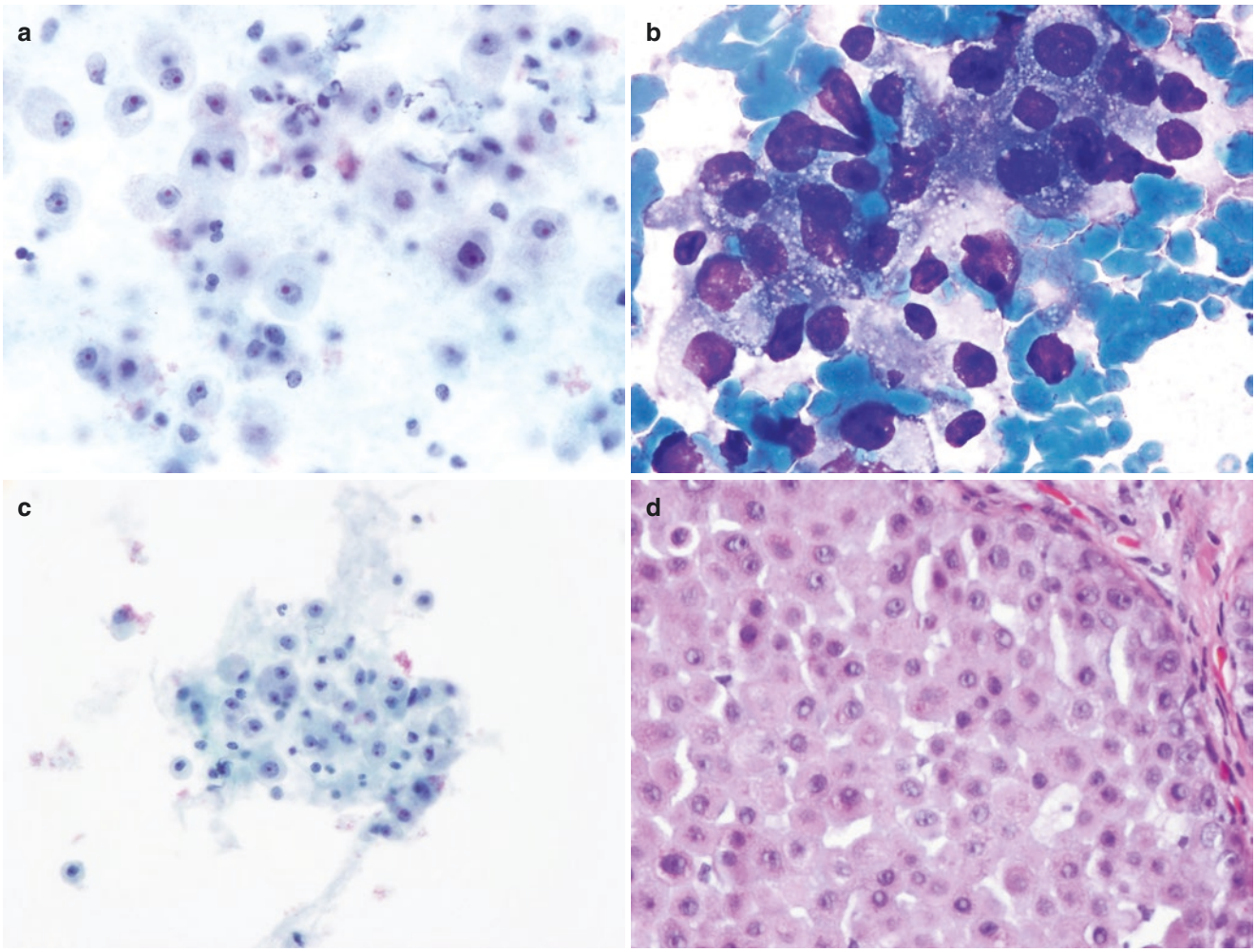


Fig. 4.12 IDC, Apocrine type: (**a**) Loosely cohesive large tumor cells can be seen with a large amount of granular cytoplasm. While the abundant dense and finely vacuolated cytoplasm may give a bland appearance, the enlarged and irregular nuclei with macronucleoli seen in these cells indicate malignancy (CS, Pap); (**b**) The pleomorphic nuclei are more apparent in the DQ stain. The cytoplasm however appears both dense and finely-vacuolated (CS); (**c**) Appearance of apocrine carcinoma on the ThinPrep slide is similar to the Pap-stained conventional smear (Pap); (**d**) The granular eosinophilic cytoplasm can be better appreciated on the resection specimen (H&E)

4.8.2.5 Metaplastic Carcinoma

Metaplastic carcinoma is a high-grade tumor that is considered to represent patterns of gene expression rather than histiogenesis, a conclusion supported by the presence of p53 gene mutation in several components of metaplastic carcinoma [1]. The tumor comprises <1% of infiltrating breast carcinoma, and clinically presents as a large tumor without axillary lymph node involvement. Metaplastic carcinoma can be divided into two categories based on histologic components: squamous and heterologous or pseudosarcomatous. Differential diagnoses include both benign and neoplastic entities. The benign differential diagnoses for metaplastic carcinoma with squamous differentiation include squamous metaplasia in a sub-areolar abscess and squamous metaplasia following lumpectomy and irradiation. Clinical history, radiological features, site of the lesion, and cytologically malignant keratinized squamous cells, aid with the differential diagnoses. For metaplastic carcinoma with mesenchymal (spindle cell) differentiation, the differential diagnoses include primary breast sarcoma and angiosarcoma. Immunohistochemistry is helpful in the detection of metaplastic carcinoma. Metaplastic carcinoma should be considered in the differential diagnosis of any spindle cell tumor in the breast (Fig. 4.13) [1–3, 6, 13, 14].

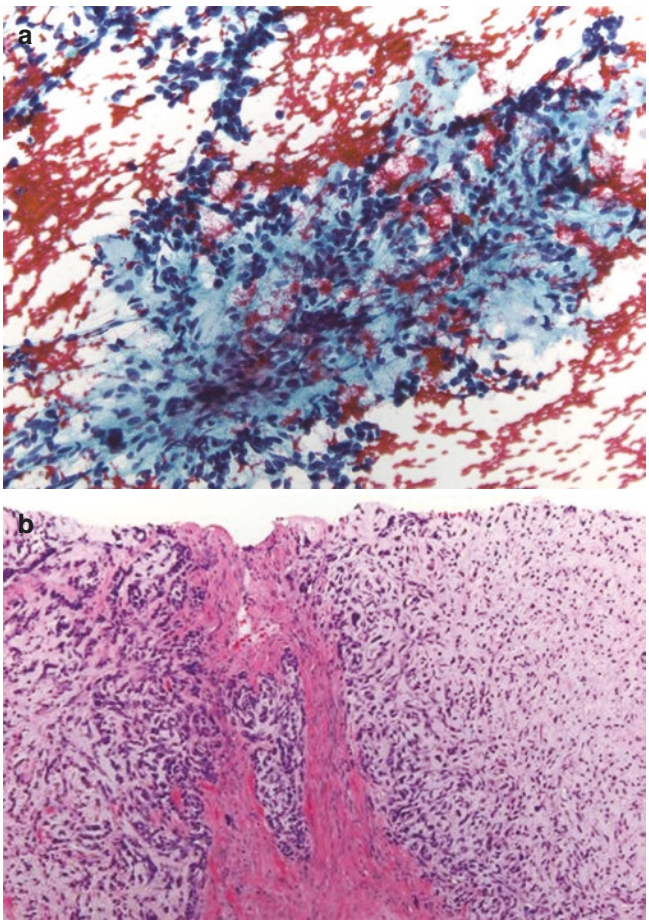


Fig. 4.13 IDC, Metaplastic type. (**a**) Ductal carcinoma of the breast can occasionally be metaplastic and contain sarcomatous elements. In this case, the carcinoma has developed an area resembling chondrosarcoma; the stroma appears light blue, the spindled cells have enlarged, overlapping nuclei, and are disorganized (CS, Pap). (**b**) Corresponding excisional biopsy shows numerous pleomorphic spindle cells present within a chondroid matrix (H&E)

4.8.2.6 Medullary Carcinoma

Medullary carcinoma is a "well-circumscribed" carcinoma composed of large poorly-differentiated cells with scant stroma and prominent lymphoid infiltration [1]. It accounts for <5% of all breast carcinomas. Histologic features include tumor cells in syncytial sheets with high nuclear grade, lymphoplasmacytic infiltration, and high mitotic rate. A definitive diagnosis of medullary carcinoma cannot be rendered on FNA or NCB because of limited sample. However, a possibility of the tumor should be suggested. Clinical differential diagnosis of medullary carcinoma includes a fibroadenoma because of the circumscribed nature of the tumor. Pathologic differential diagnoses include chronic mastitis, intramammary lymph node, and lymphoma of the breast. The benign entities are distinguished from medullary carcinoma by the absence of tumor cells. Lymphoma lacks the syncytial arrangement or loosely-cohesive clusters of tumor cells. Immunohistochemistry can be applied. The distinction between medullary carcinoma and poorly differentiated NST type is also not possible on FNA and NCB. This is an important distinction with prognostic implications, as the former has a better overall prognosis (Fig. 4.14) [1–3, 6, 13].

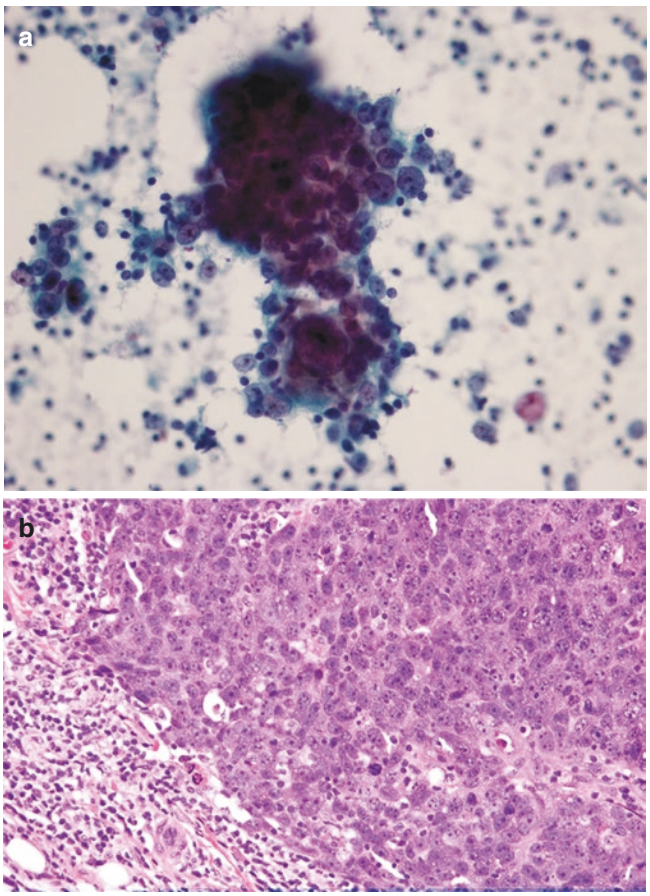
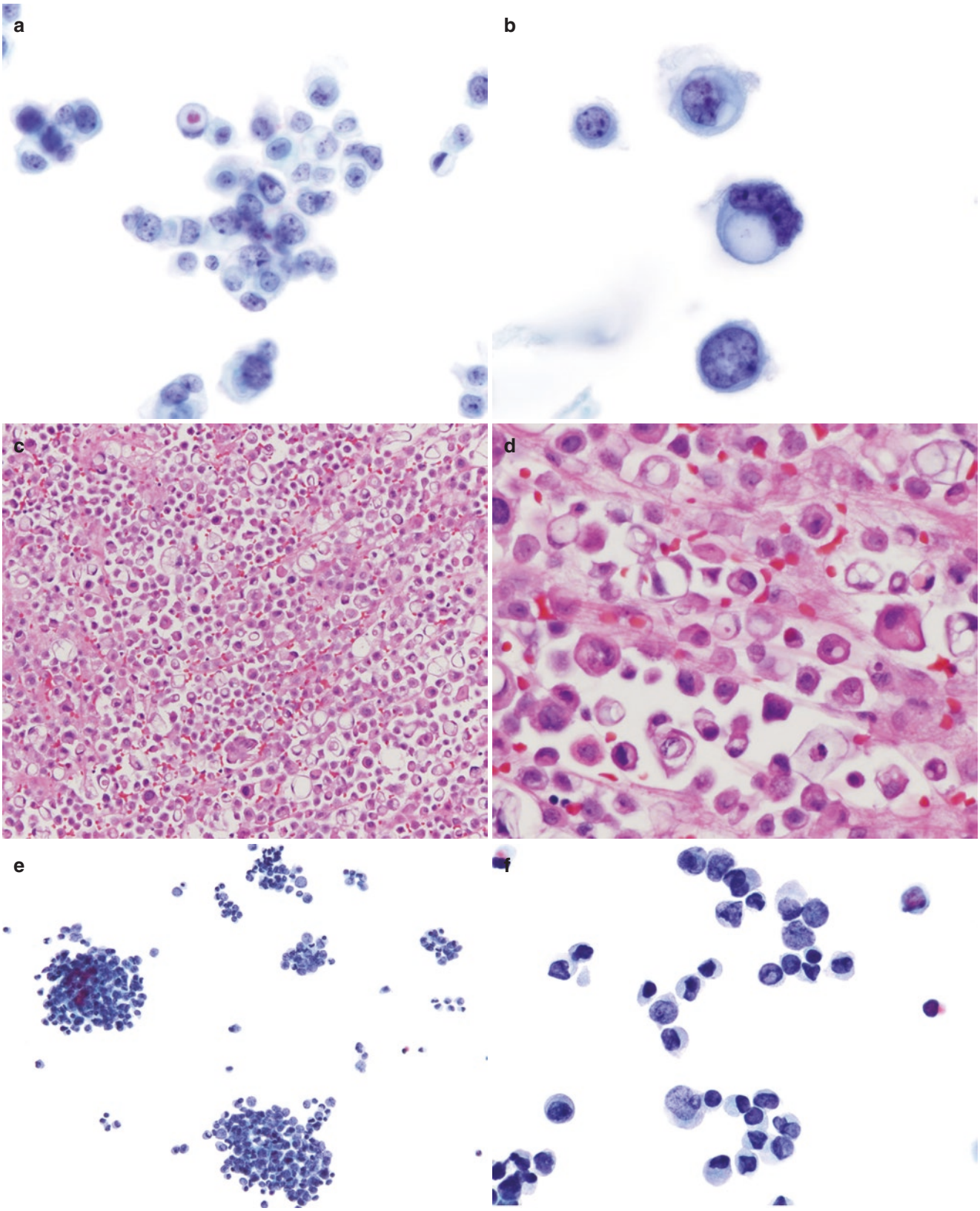


Fig. 4.14 Medullary carcinoma: (**a**) The tumor cells are arranged singly and in clusters of large undifferentiated cells with markedly enlarged and overlapping nuclei, variation in nuclear size, marked nuclear border irregularities, and prominent nucleoli. Small mature lymphocytes can be seen admixed within the tumor cell groups (CS, UF-Pap); (**b**) Markedly pleomorphic tumor cells with similar cytology as described above surrounded by small mature lymphocytes on the resection (H&E)

4.8.3 Invasive Lobular Carcinoma

Invasive lobular carcinoma (ILC), with classic and variant histologic appearance, accounts for approximately 5–14% of all invasive breast carcinomas. These tumors occur at all age ranges, but are more common in older women. Clinical presentation is usually a mass with ill-defined margins. It may also present as a vague thickening or nodularity of the breast. Patients with ILC have a relatively high frequency of bilateral disease when compared with other types of invasive carcinomas. Histologically, ILC shows a linear (cords of cells) and swirling pattern of growth with lack of solid, papillary, and glandular patterns. The tumor cells are fairly monotonous, small, and uniform, and may be mistaken for inflammatory cells. The nuclei are eccentrically placed and uniform with inconspicuous nucleoli. Tumor cells can also exhibit mucin-rich intracytoplasmic vacuoles that impart a signet-ring appearance to the cells. The linear pattern of tumor cells is likened to an "Indian file." Cytological features are similar to those described for histology. In pleomorphic lobular carcinoma, the tumor cells are large with abundant apocrine-type cytoplasm and relatively enlarged hyperchromatic nuclei. Cytologic diagnosis of ILC is one of the most common causes of false-negative FNA due to scant cellularity of tumor cells and small tumor cell size (Fig. 4.15) [1–3, 6, 15, 16].

Fig. 4.15 Invasive lobular carcinoma (ILC), classic type: (**a**) Small carcinoma cells with little cytoplasm can be seen in loosely-cohesive sheets or singly in an otherwise clean background. The linear "Indian-file" pattern of growth is obvious. The nuclear borders are irregular, with moderate variation in shapes and sizes. In clustered cell groups, the nuclei seem to "mold." Appearance of lobular carcinoma is similar to conventional smears (TP, Pap); (**b**) While cytoplasmic vacuoles are not always present, some cells have large vacuoles that give the cells a "signet ring" appearance (the nucleus is compressed to the periphery by the vacuole). In this field, one cell contains condensed mucin which has stained pink on Pap stain (TP, Pap); (**c**) On surgical pathology, the neoplastic cells are loosely cohesive and enlarged when compared to adjacent red blood cells. Some cells have prominent nucleoli and most have an eccentrically placed nucleus. The cytoplasm is foamy, with some cells showing mucin vacuoles (H&E); (**d**) In this surgical pathology section, some cells have prominent nucleoli and most have an eccentrically placed nucleus. The cytoplasm is foamy, with some cells showing mucin vacuoles and eccentrically placed compressed nucleus imparting a "signet ring"-like appearance (H&E); (**e**) ILC, pleomorphic type: The TP is cellular and the cells are arranged predominantly in a dyshesive pattern, occasionally forming a few, small aggregates. Note the prominent linear pattern of growth "Indian-file" pattern. Tumor cells display significant nuclear pleomorphism, membrane irregularity, prominent nucleoli, and abnormal chromatin distribution. Cytoplasm is abundant, pale-to-eosinophilic, and can be granular or vacuolated (TP, Pap); (**f**) ILC, pleomorphic type: Cellular aspirate with predominantly dyshesive malignant cells, occasionally forming small aggregates but mostly as single cells. Note the prominent linear pattern of growth ("Indian-file") pattern. The tumor cells as seen here are pleomorphic, enlarged, with relatively-enlarged nuclei, prominent nucleoli. and abundant cytoplasm. Occasional multinucleated malignant cells can be seen and mitoses can be frequent (TP, Pap)


a
b
c
d
e
f

4.9 Papillary Lesions/Neoplasms

Papillary neoplasms of the breast include a wide spectrum of mammary lesions, both benign and malignant, the differential diagnosis of which can be problematic not only in FNA but also in NCB. A diagnosis of an intraductal papilloma or papillary carcinoma on these two modalities warrants surgical excision. Immunostains for smooth muscle actin, calponin, or p63 may be useful in identifying myoepithelial cells, which may favor papilloma [1–3, 6, 13, 17].

4.9.1 Intraductal Papilloma

Central solitary papilloma is a discrete benign papillary tumor that arises from a lactiferous duct usually from the central part of the breast. Clinically, it presents as a palpable subareolar mass. Central solitary papilloma can occur at any age and are usually associated with a nipple discharge that is more commonly non-bloody. Histologically, the papilloma comprises of branching fronds of stroma lined by a layer of cuboidal to columnar epithelium and myoepithelium. The stroma contains thin-walled capillaries and histiocytes. Papilloma can also become complex. Cytologically, pseudopapillary or papillary structures and cell balls, comprising columnar-to-round ductal cells, can be seen. Background is either proteinaceous or bloody and contains macrophages (Fig. 4.16) [1–3, 6, 14].

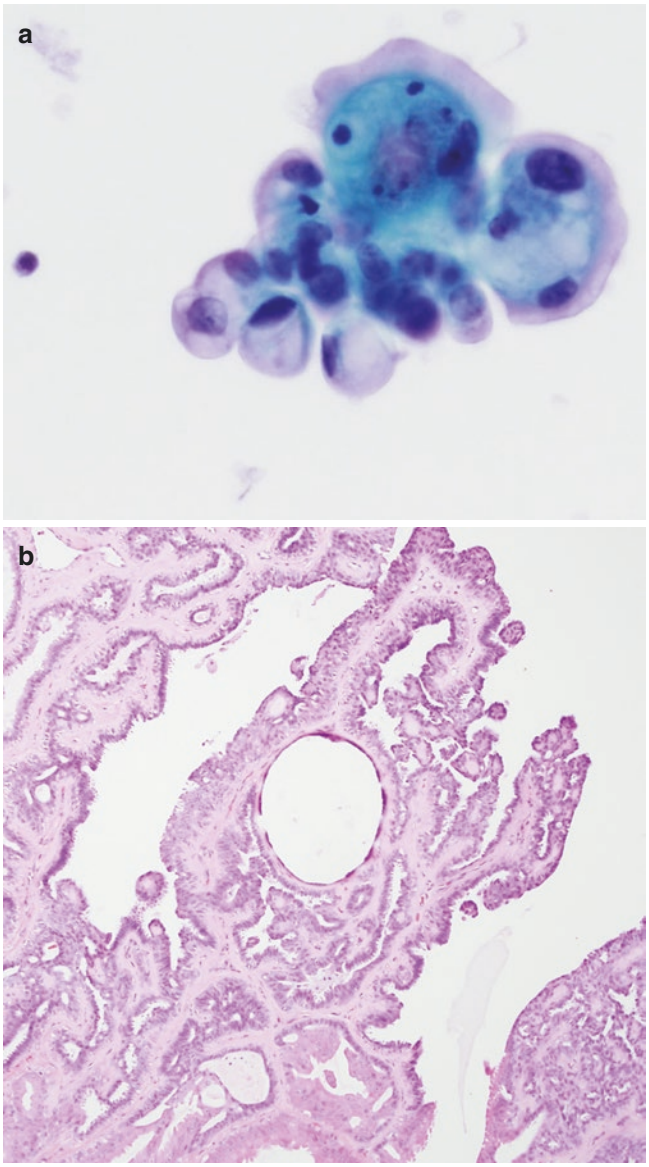
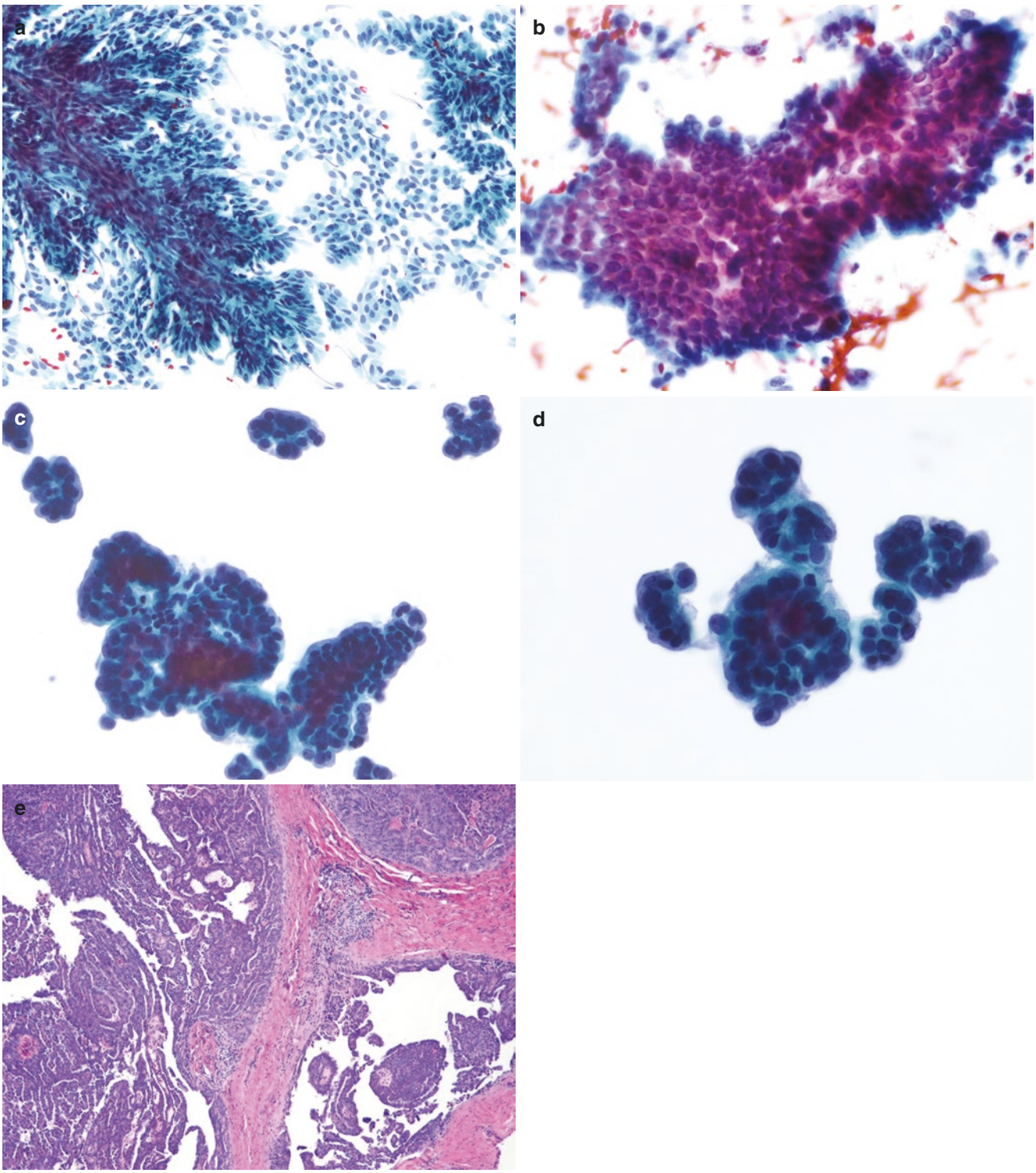


Fig. 4.16 Intraductal papilloma: (**a**) Intraductal papilloma tend to occur as solitary retroareolar tumors but can also occur anywhere in the breast. On FNA, the cells are cuboidal-to-columnar and arranged in a papillary-like cluster or in a cell ball, as shown here. The nuclei are round and regular with fine chromatin and small nucleoli. Note the cytoplasmic vacuolation (TP, Pap); (**b**) The corresponding excisional biopsy shows an intraductal papilloma with multiple papillae containing vascularized fibroconnective tissue. Apocrine metaplasia can be seen (H&E)

Fig. 4.17 Papillary carcinoma: (**a**) This CS shows a very cellular specimen with columnar cells, many of which are loosely attached to thin fibrovascular cores with complex branching. The monotony of these cells and the bland nuclear features may not suggest carcinoma; however, the specimen is hypercellular, and lacks obvious myoepithelial cells. Note the many isolated columnar cells in the background (CS, Pap); (**b**) Papillary carcinoma shows tumor cell clusters with a papillary-like configuration. The columnar cells are well appreciated at the edges of the cell clusters. Differentiating between benign and malignant papillary lesions on FNA and NCB can be challenging (CS, Pap); (**c**) Papillary carcinoma on ThinPrep show complex and cellular papillary-like clusters with columnar cells arranged around the edges. The nuclei demonstrate hyperchromasia, anisonucleosis, and overlapping. The LBP shows few or no single epithelial cells and the background appears clean and less bloody as opposed to the CS (Pap stain). (**d**) Another case of papillary carcinoma on LBP. Note the clean background with few or no single epithelial cells and less blood as opposed to the CS (TP, Pap)

4.9.2 Papillary Carcinoma

Papillary carcinoma comprises 1–2% of all breast carcinomas. It is a term used for carcinomas that histologically show frond formation. The main distinguishing features between a papilloma and papillary carcinoma are: in papillary carcinoma the predominant growth pattern is frond-like papillae with less evenly-distributed and more complex fibrovascular cores compared to papilloma; the epithelial cells are less orderly, nuclei are hyperchromatic with uneven chromatin distribution and have high N:C ratio compared to papilloma; myoepithelial cells are absent in papillary carcinoma but uniformly present in papilloma; and lastly, mitoses are more frequent in papillary carcinoma (Fig. 4.17) [1–3, 6, 13].



4.10 Role of Immunohistochemistry in Breast Carcinoma

Immunohistochemical staining for breast markers in cytology preparations is usually performed to confirm metastatic breast carcinoma, to evaluate the predictive/prognostic markers in metastatic breast carcinoma, and to distinguish between ductal versus lobular carcinoma**.**

4.10.1 Metastatic Breast Carcinoma

Metastatic breast carcinoma, both NST and lobular types, is one of the most common metastases analyzed in any cytology laboratory. The common sites for metastatic breast carcinoma are bone, lungs, and liver [1–3]. Immunohistochemistry (IHC), specific to breast carcinoma and to the organ where the metastasis is detected, can be performed on CB sections, conventional smears, or LBP for diagnosis (Figs. 4.18, 4.19, and 4.20) [1–3, 6, 18, 19]. The markers commonly used in practice to confirm a malignancy of breast origin include GATA-3, GCDFP15, and mammaglobin. Of these three markers, GATA-3 offers the most sensitivity, up to 94%, and high specificity, especially for tumors that are ER positive as well. GATA-3 is a zinc binding transcription factor that regulates the differentiation of many human tissue types, including the mammary gland, and shows positive staining of the tumor cell nuclei. Although the sensitivity of GATA-3 in triple negative breast cancers (TNBC) is significantly lower than in non-TNBC, it still has added value in the work up of metastatic TNBC because ER, PR, and HER-2 immunostains ideally cannot serve as markers for detection of these tumors. Approximately 40–70% of breast carcinomas are GCDFP-15 positive, and 60–80% express mammaglobin. In the workup of metastases of unknown primary or metastases from a TNBC, a panel of these three immunostains is suggested for a thorough evaluation.

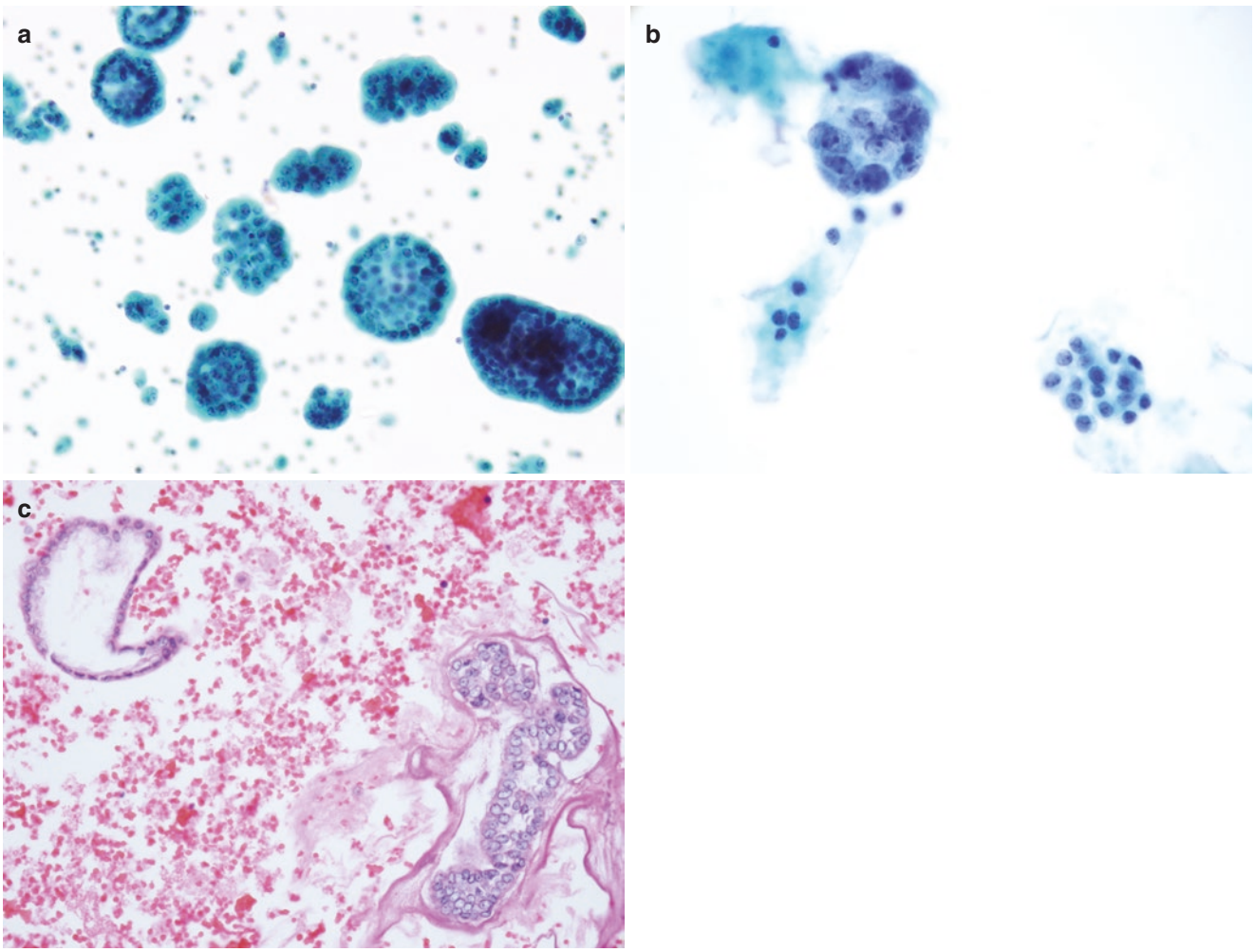


Fig. 4.18 Metastatic ductal carcinoma of breast in pleural effusion: (**a**) In body cavity fluids, including pleural, pericardial, and peritoneal effusions and cerebrospinal fluid (CSF), metastatic breast carcinoma may reveal several patterns. Tumor cells of metastatic ductal carcinoma may form a 3-D "cannon ball" clusters or "morula," as seen here. The cells in the periphery of these tumor cell clusters have a columnar configuration. The contours of the cell spheres are smooth (community borders) in contrast to the scalloped borders seen in mesothelial cell proliferations. In this SurePath LBP, the background shows some inflammatory cells and benign mesothelial cells, in a different plane of focus than the tumor cells (Pap stain); (**b**) Another case of metastatic ductal carcinoma of breast in pleural effusion on ThinPrep LBP shows similar cohesive clusters of tumor cells or morula with markedly enlarged nuclei, hyperchromasia, and prominent nucleoli. Compare the nuclear size of the malignant tumor cells with those of the lymphocytes and benign mesothelial cells in the background. Note that the background elements are present on the similar plane of focus as the tumor cells. These tumor cell clusters lack the "windows" between the cells, which is a feature typically seen in benign mesothelial cell clusters (Pap stain); (**c**) Metastatic ductal carcinoma of breast in pleural effusion on the CB section shows a group of metastatic ductal carcinoma cells (bottom right) with similar cytomorphology as described previously. Also appreciate the benign mesothelial cell cluster (top left) (H&E)

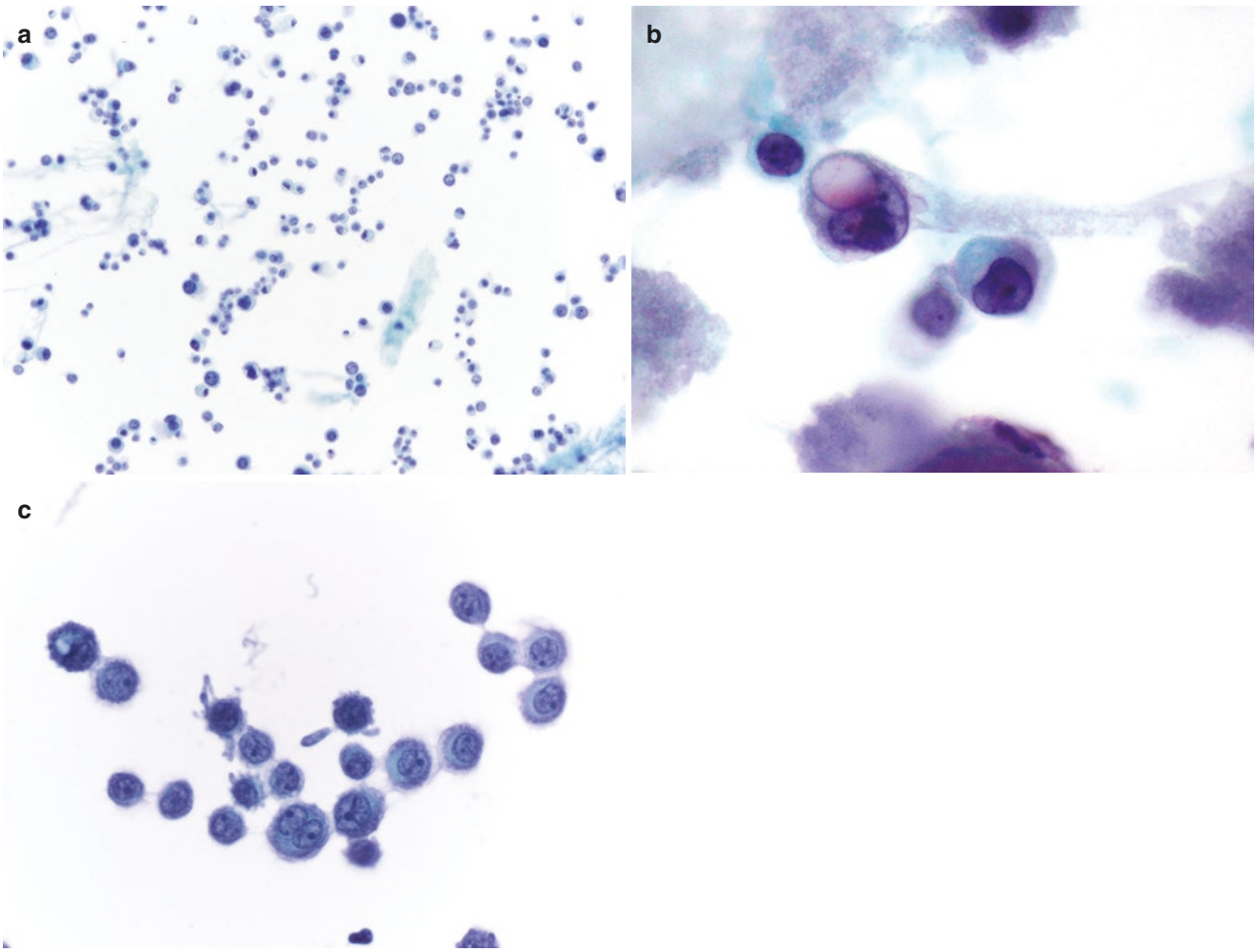


Fig. 4.19 Metastatic lobular carcinoma of breast in peritoneal effusion: (**a**) Lobular carcinoma in body cavity fluids have a predominant single-cell appearance as seen here with hyperchromatic enlarged nuclei, scanty cytoplasm, and conspicuous nucleoli. Single-file configuration and bull's-eye arrangement serve as basic patterns. The low cellularity of lobular carcinoma in fluid could lead to a potential pitfall in diagnosis due to bland cytology of tumor cells. Lobular carcinoma cells may be difficult to distinguish from reactive mesothelial cells or inflammatory cells (TP, Pap). (**b**) On higher magnification one can appreciate occasional cells with signet ring-like morphology with eccentrically placed enlarged and hyperchromatic nuclei and a prominent mucin vacuole. The background shows moderately abundant blood (TP, Pap). (**c**) Metastatic lobular carcinoma in CSF presents mostly as single cells with similar cytology as seen in lobular carcinoma elsewhere. The cytologic features include linear cell arrangement, enlarged hyperchromatic nuclei, increased N;C ratio, irregular nuclear membranes and a vacuolated cytoplasm (Cytospin, Pap stain)

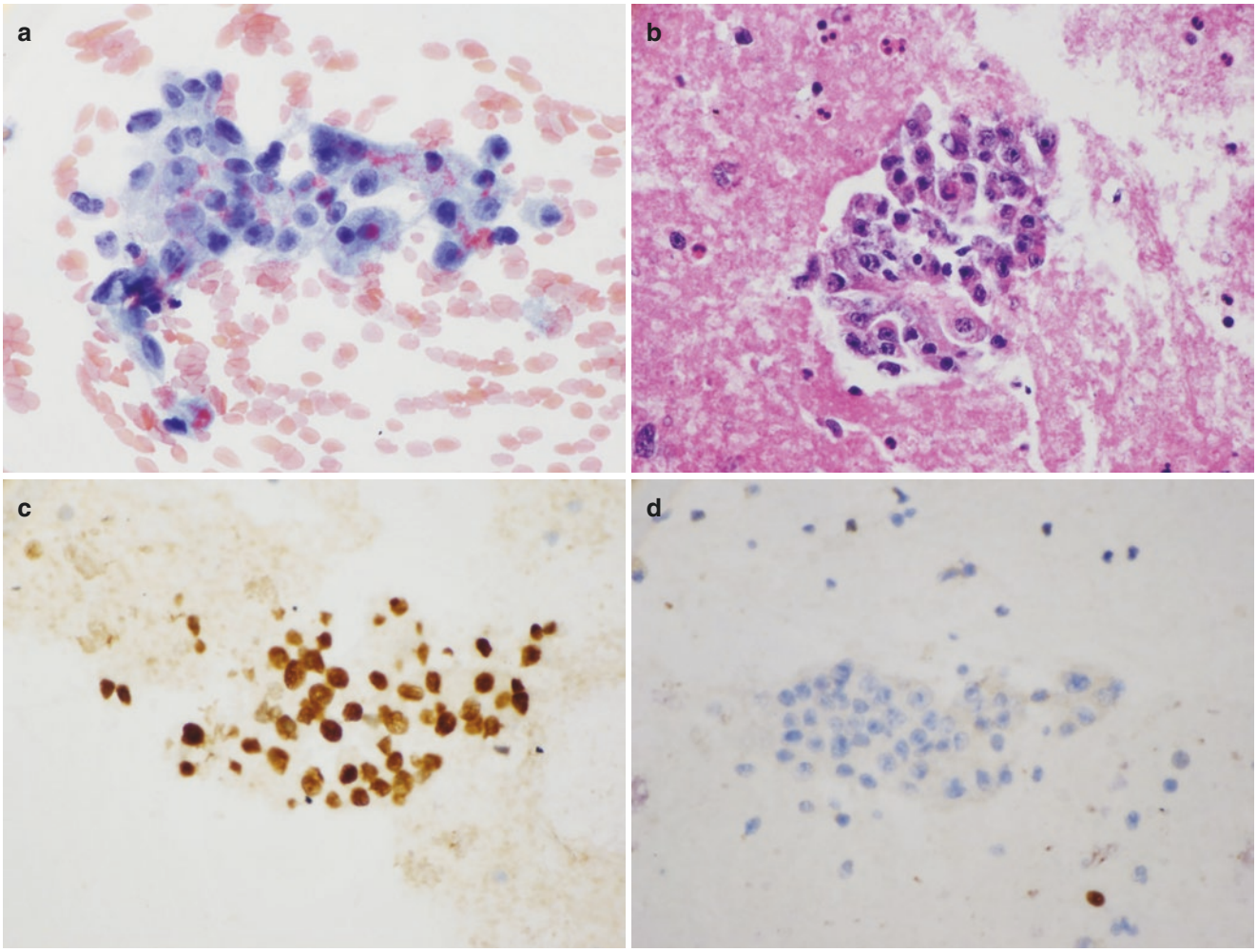


Fig. 4.20 Metastatic apocrine carcinoma of breast to thyroid gland: (**a**) Morphology is similar to that described for apocrine carcinoma of the breast (Fig. 4.12a). In this case, the differential diagnosis was primary Hurthle cell neoplasm of thyroid. However, the clinical history and type of breast carcinoma were known (CS, Pap stain); (**b**) CB section showing similar features to those described before in Fig. 4.12b; (**c**) Immunostain for GATA-3 showed positive nuclear staining (CB); (**d**) Immunostain for TTF-1 was negative (CB). Thyroid molecular test, ThyroSeq (University of Pittsburgh Medical Center, Pittsburgh, PA and CBLPath, Rye Brook, NY, collaborative test) failed to show any thyroid neoplasm-associated genes and the genetic abnormalities supported metastasis to thyroid

4.10.2 Predictive/Prognostic Markers in Breast Carcinoma

With therapeutic advances, breast cancer patients are having better survival, with some showing late recurrences. As pathologists play an increasing role in the era of personalized medicine, it has become more common to test for estrogen receptor (ER), progesterone receptor (PR), and HER2/neu expression in patients with known recurrent or metastatic breast carcinoma. Testing for ER, PR, and HER 2 by IHC has been developed and optimized for use on formalin-fixed paraffin-embedded (FFPE) tissue obtained by incisional/excisional biopsies or resection specimens. HER 2/neu and the ER and PR status are important prognostic and predictive factors in the management of patients with breast carcinoma. Studies on the immunocytochemical analysis of ER, PR, and HER 2/neu on conventional smears, touch preparations, cytospins, and LBP, with different fixation methods and with different antibodies, have shown conflicting results, particularly for HER 2/neu. The prevailing recommendations and contemporary practices of breast FNA caution against the use of cytology smears and cytospins for ancillary testing unless the laboratory has specific protocols for IHC on cytologic material and they recommend use of CB sections, as they are analogous to surgical pathology material. Studies have shown that IHC for HER 2/neu, ER, and PR performed on FFPE cell blocks, prepared from fresh FNA and serous effusions, is reliable in predicting the expression of these markers when correlated with IHC and/or FISH performed on the corresponding histological specimens [20].

4.10.3 Distinguishing Between NST Versus Lobular Carcinoma

Lobular and NST type of carcinomas have distinctly different clinical behaviors and prognostic implications; distinguishing these lesions on cytology is therefore critical for patient management. The most common molecular alteration in lobular carcinoma is the complete loss of E-Cadherin expression [21]. More than 85% of NST type of carcinoma cells show strong membranous staining, whereas more than 85% of lobular carcinoma cells show loss of E-Cadherin. In addition, reduced or impaired E-Cadherin expression is associated with reduced disease-free interval and overall survival. Another marker useful in this distinction between lobular versus NST type of carcinoma is p120 catenin, which binds within the internal surface of the cell membrane to form a cadherin-catenin complex. p120 catenin demonstrates membranous staining in NST type lesions and diffuse cytoplasmic staining in lobular lesions and is very helpful especially in lobular carcinoma manifesting as single cells in the preparation.

4.11 Metastatic Non-mammary Tumors to the Breast

Metastases to breast account for approximately 1.3–3% of malignant mammary tumors [1, 22]. The most commonly reported primary tumors to metastasize to the breast include hematopoietic neoplasms, malignant melanoma, and small cell carcinoma of the lung. The average interval between non-mammary (primary) tumor diagnosis and development of metastatic disease in the breast is around 2 years. In approximately one-third of patients, a breast mass may be the initial clinical presentation of the non-mammary primary. It is more common for a disseminated tumor to involve the breast as a component of systemic spread. An accurate diagnosis of breast metastases is important for optimal therapy and avoidance of unnecessary surgery. Clinical history and knowledge of prior non-mammary malignancy are very important factors in establishing a diagnosis of a metastatic tumor. The radiologic feature of microcalcifications favors a breast primary. Pathological assessment on FNA and NCB with immunohistochemistry are important in distinguishing between metastatic versus breast primary (Fig. 4.21) [1, 22].

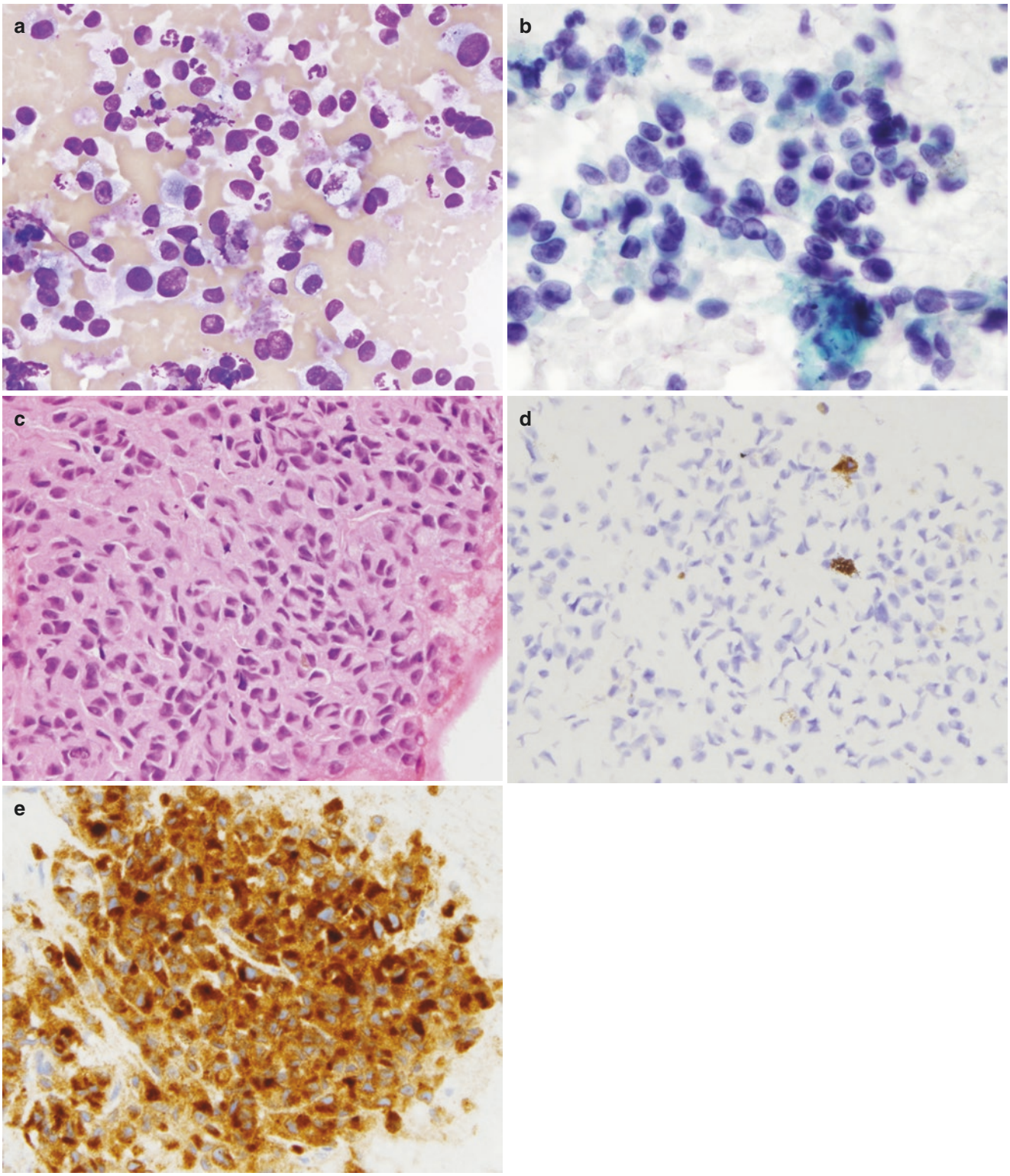


Fig. 4.21 Metastatic melanoma to the breast: (**a**) Isolated cells with eccentrically placed, enlarged and irregular nuclei with prominent nucleoli and finely vacuolated-to-dense cytoplasm. Occasional binucleated cells are present. A linear pattern of cell arrangement is noted at bottom right of the image. Differential diagnoses include pleomorphic lobular carcinoma and high-grade lymphoma (CS, DQ stain); (**b**) Note the macronucleoli and an intranuclear inclusion at the 8 o'clock position. N:C ratio is high (CS, Pap stain); (**c**) Histology of melanoma (resection, H&E); (**d**) The infiltrating tumor was cytokeratin negative (CB); (**e**) The tumor was immunoreactive for melanoma markers, HMB-45, S-100, SOX-10 and Melan-A (CB, HMB-45)

References

1. Hoda SA, Brogi E, Koerner FC, Rosen PP. Rosen's diagnosis of breast pathology by needle core biopsy. 4th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2016.
2. Dong J, Ly A, Arpin R, Ahmed Q, Brachtel E. Breast fine needle aspiration continues to be relevant in a large academic medical center: experience from Massachusetts General Hospital. Breast Cancer Res Treat. 2016;158:297–305.
3. Ly A, Ono JC, Hughes KS, Pitman MB, Balassanian R. Fine-needle aspiration biopsy of palpable breast masses: patterns of clinical use and patient experience. J Natl Compr Cancer Netw. 2016;14:527–36.
4. Topps AR, Barr SP, Pikoulas P, Pritchard SA, Maxwell AJ. Pre-operative axillary ultrasound-guided needle sampling in breast cancer: comparing the sensitivity of fine needle aspiration cytology and core needle biopsy. Ann Surg Oncol. 2018;25:148–53.
5. Kwak JY, Kim EK, Park HL, Kim JY, Oh KK. Application of the breast imaging reporting and data system final assessment system in sonography of palpable breast lesions and reconsideration of the modified triple test. J Ultrasound Med. 2006;25:1255–61.
6. Hoda RS. Non-gynecologic cytology on liquid-based preparations: a morphologic review of facts and artifacts. Diagn Cytopathol. 2007;35:621–34.
7. Alwahaibi NY, Alsubhi MS, Aldairi N, Alshukaili A, Bai UR. Comparison of ultrafast papanicolaou stain with the standard papanicolaou stain in body fluids and fine needle aspiration specimens. J Lab Phys. 2016;8:19–24.
8. Arul P, Masilamani S. Application of National Cancer Institute recommended terminology in breast cytology. J Cancer Res Ther. 2017;13:91–6.
9. Field AS. Breast FNA biopsy cytology: current problems and the International Academy of Cytology Yokohama standardized reporting system. Cancer. 2017;125:229–30.
10. Ly TY, Barnes PJ, MacIntosh RF. Fine-needle aspiration cytology of mammary fibroadenoma: a comparison of ThinPrep® and Cytospin preparations. Diagn Cytopathol. 2011;39:181–7.
11. Heymann JJ, Halligan AM, Hoda SA, Facey KE, Hoda RS. Fine needle aspiration of breast masses in pregnant and lactating women: experience with 28 cases emphasizing ThinPrep findings. Diagn Cytopathol. 2015;43:188–94.
12. Yu SN, Li J, Wong SI, Tsang JYS, Ni YB, Chen J, et al. Atypical aspirates of the breast: a dilemma in current cytology practice. J Clin Pathol. 2017;70:1024–32.
13. Haji BE, Das DK, Al-Ayadhy B, Pathan SK, George SG, Mallik MK, et al. Fine-needle aspiration cytologic features of four special types of breast cancers: mucinous, medullary, apocrine, and papillary. Diagn Cytopathol. 2007;35:408–16.
14. Jha A, Agrawal V, Tanveer N, Khullar R. Metaplastic breast carcinoma presenting as benign breast lump. J Cancer Res Ther. 2017;13:593–6.
15. Green KM, Turyan HV, Jones JB, Hoda RS. Metastatic lobular carcinoma in a ThinPrep Pap test: cytomorphology and differential diagnosis. Diagn Cytopathol. 2005;33:58–9.
16. Ohashi R, Matsubara M, Watarai Y, Yanagihara K, Yamashita K, Tsuchiya SI, et al. Pleomorphic lobular carcinoma of the breast: a comparison of cytopathological features with other lobular carcinoma variants. Cytopathology. 2017;28:122–30.
17. Michael CW, Buschmann B. Can true papillary neoplasms of breast and their mimickers be accurately classified by cytology? Cancer. 2002;96:92–100.
18. Plonczak AM, DiMarco AN, Dina R, Gujral DM, Palazzo FF. Breast cancer metastases to the thyroid gland – an uncommon sentinel for diffuse metastatic disease: a case report and review of the literature. J Med Case Rep. 2017;11:269.
19. Rao R, Hoda SA, Marcus A, Hoda RS. Metastatic breast carcinoma in cerebrospinal fluid: a cytopathological review of 15 cases. Breast J. 2017;23:456–60.
20. Shabaik A, Lin G, Peterson M, Hasteh F, Tipps A, Datnow B, et al. Reliability of Her2/neu, estrogen receptor, and progesterone receptor testing by immunohistochemistry on cell block of FNA and serous effusions from patients with primary and metastatic breast carcinoma. Diagn Cytopathol. 2011;39:328–32.
21. Peng Y, Butt YM, Chen B, Zhang X, Tang P. Update on immunohistochemical analysis in breast lesions. Arch Pathol Lab Med. 2017;141(8):1033–51.
22. Georgiannos SN, Chin J, Goode AW, Sheaff M. Secondary neoplasms of the breast: a survey of the 20th century. Cancer. 2001;92:2259–66.